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# THE MEDICAL JOURNAL OF AUSTRALIA

VOL. II.—42ND YEAR

SYDNEY, SATURDAY, OCTOBER 29, 1955

No. 18



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### THE DEVELOPMENT OF MODERN PSYCHIATRY IN RELATION TO MEDICINE AND SURGERY.<sup>1</sup>

By H. B. RUDDUCK,  
Melbourne.

FROM the earliest known times attempts have been made to assist those suffering from mental illness, but it is only recently that the condition has been understood and rational treatment given. In olden times mental patients received very harsh treatment from well-meaning but mistaken individuals. At one period, torture, violence and shocks were given. Patients were blistered, purged and bled. Of late there has been a considerable change in treatment, as well as in the understanding of those requiring it.

It is becoming more apparent that most cases of mental illness arise through no fault of the patient, and considerate treatment, education and reassurance are better therapeutic measures than those formerly used.

Latterly there has been a shift towards preventive rather than curative treatment, and to the treatment of groups—social psychiatry—in addition to that of the individual.

<sup>1</sup> A shortened form of the Stawell Prize Essay for 1955, presented under the *nom de plume* "Aum mani padme hum", a Tibetan prayer of which the following is a free translation: "May those in authority look upon my meditation with understanding and grant my deepest wish."

Not a small factor in these changes has been the knowledge, comparatively recently acquired, that mental illness (particularly neuroses) is much more widespread than was previously realized. Many border-line cases exist, and nobody whose family tree is complete for several generations is completely unrelated to someone with a mental disorder of some kind. Perhaps this changing attitude of the general populace to the mental patient is one of the greatest therapeutic advances of psychiatry.

In considering the development of psychiatric treatment it is convenient to divide the methods used into two classes, according to their mode of origin. The first group is that having a scientific basis; it has arisen mainly, but not entirely, from the rational method of finding the cause and then treating the patient accordingly. In this group is to be considered treatment of general conditions along the usual medical lines adopted for fevers, infections and trauma, as well as dietetic and hygienic procedures. The use of endocrine and latterly antibiotic agents is another part of this group. Included, too, are thermal treatment and treatment with malaria for general paralysis of the insane.

Drugs, such as sedatives, to lessen mental activity have been used to enforce rest. Up to twenty hours' sleep a day for five to ten days has been of considerable value in certain cases. The stimulant amphetamine, which increases mental alertness and temporarily diminishes fatigue, has helped in cases of minor depression and irritability.

A recent advance from this section is the employment of synthetic anti-convulsants—for example, "Dilantin", "Tridione", "Mysoline"—in the treatment of epileptic patients. The administration of "Antabuse", whose action is biochemical, is, with other treatment, now a recognized treatment for alcoholics.

These methods, as well as general medical measures—rest, exercise, attention to general health, hygiene and diet—have their value in certain types of mental illness.

The second group of therapeutic agents are those that have been developed along empirical lines. In spite of their mode of origin, the members of this group include some of the most valuable means of treatment at the psychiatrist's disposal. Probably the most important of this group are those methods of treatment derived from Freud's theories. From these he developed psychoanalysis, through which complexes are detected and resistances overcome. Freud commenced by using hypnotic methods, but came to develop free association, because he found it to be satisfactorily applied to a larger number of patients. Psychoanalysis by free association has two serious drawbacks. One is the length of time taken, the other the difficulty in overcoming resistances.

Hypnosis is of value against both these factors. It enables complexes to be more rapidly defined and assists the patient to master resistances. Automatic writing, crystal-gazing, regression to an earlier age and revivification are procedures that may be used during hypnosis to recall repressed memories; while the technique of delayed recall is another valuable development, since it allows time for some adjustment by which the ego prepares itself for the memory.

Resistances are less powerful when the patient is dreaming or as he is awakening from sleep. Psychiatric investigation has learnt to take advantage of these periods. Chemicals and drugs have been used to overcome resistances. Included here are the use of ether, anaesthesia and deep sedation with barbiturates, chloral or other agents.

In the treatment of an emotional problem by psychotherapy, at first the objective was to remove the symptom which brought the patient for treatment; but it was soon apparent that emotional problems have an extensive basis which is rarely restricted to one symptom. Investigation of the patient usually reveals many other abnormal conditions which have been brought about by causes unknown to the patient. When the conditions are favourable, treatment is now directed to the readjustment of the basal abnormalities, by giving the patient an understanding of his conscious and subconscious mind and showing him the connexion between his emotional upset and the symptoms it produces. The more superficial form of treatment, in which the symptoms are removed without getting to the root of the trouble, may be the only method practicable in certain cases.

A further development in the treatment of psychiatric conditions, particularly the functional ones, has been the establishment of teams of workers cooperating in the patient's welfare; such a team may consist of a clinician, a specialized social worker, a clinical psychologist and a psychiatrist.

There are three separate methods of treatment that may be considered together because they have at least three points in common. Each arose from accident rather than design. Each produces valuable or even dramatic results in suitable cases. In none of the methods is the mode of action fully understood. Explanation of how the action occurs has come after, not before, the adoption of the method as a means of treatment.

Insulin therapy developed from the study of drug addiction by Sakel, who found small doses of insulin beneficial both in increasing appetite and in reducing mental tension during withdrawal of the drug causing addiction. He extended its use to other mental disorders and increased the dose used. Now large quantities, carefully employed, render the patient unconscious for periods of up to an hour, and the treatment may be repeated daily. This therapy is of great value in paranoid schizophrenia.

Electro-convulsive therapy resulted from the observation of Nyiro that epilepsy was not seen so often in patients with schizophrenia as one would expect. He considered that the two conditions opposed each other. From this deduction Meduna came to use artificially induced epileptic convulsions for schizophrenic patients. Both the means of producing the convulsions and the disorders for which the method is employed have departed somewhat from the original. At first drugs were used, but this has been succeeded by electrical methods. A further change has been the control of the severity of the convulsions by anaesthetic means, and later their elimination by curare. This therapy is now considered valuable, not only in schizophrenia, but also in psychotic depression, as well as in depression associated with conditions other than melancholia—for example, general paralysis of the insane or neurosis.

Leucotomy, the third therapeutic measure of the group, owes much of its origin to an accident in which a person had portion of his brain destroyed by a crowbar. Recovery took place, and the carefully recorded medical history of this patient led to conclusions of value in formulating the extent of the leucotomy operation and its probable effect upon the patient. An intermediate step in the development of this operation was the use of trained apes for experimental purposes, before the method was adopted for human use. This point indicates how comparative studies may be used in the development of psychiatry. Leucotomy is indicated for the relief of anxiety, tension, depression and even physical pain in certain cases. The serious consequences which may follow restrict its use to cases in which other treatment has failed.

The inability to understand precisely how these three methods of treatment act in certain mental disorders, and the incapacity to appreciate completely functional nervous disease, indicate how inadequate is the knowledge so far available of mental function and abnormalities of the mind. Although a great deal is known there is still much to be learnt, and those interested are constantly striving to add to the accepted facts. One way of making a definite advance is to correlate the less precise information obtained from a vague subject with data accepted by the accurate scientific standards of an exact one. It is on these lines that the following personal experiences and observations are recorded and an attempt is made by rational measures to connect and explain them by neurological means.

The explanations given may not be correct; but since they are drawn from a logical basis they can be used as a starting point in a subject which does not enable one to make definite statements easily. It is hoped that if they are found untenable, they will lead to replacement by something more fitting, until ultimately the correct explanation is made clear.

The research worker had been counting the number of mitotic figures in 100 fields, dividing them into groups according to the stage of mitosis and recording the result for each 1000 cells. This he hoped to correlate with the rate of tumour growth. With both eyes open, he was able instinctively to pick out mitotic figures, to note any peculiarity of active or resting cells and to sketch this by visually projecting it on to the notebook which, for this purpose, was placed beside his microscope. After prolonged periods, he could look away from the microscope, yet still distinctly see the field on the wall, or even when his eyes were shut. He had reached this stage, but continued until the 100 fields were completed, when, provoked by fatigue, he relaxed back in his chair. He looked at his microscope and the numerical table of nuclei he had just completed. Strange how these two factors always took him back, fifteen years now, to the first time he ever looked through a microscope, this very one.

He remembered that day clearly. The demonstrator had just completed a lecture on the microscope and how to use it, in which he advised cultivating from the start the ability to keep both eyes open and to use each eye alternately. The research worker distinctly recalled how, following these instructions, he kept both eyes open and



looked down the eyepiece with his right. He clearly saw the bench on which the microscope stood. On that day no amount of trying was successful unless he covered or shut his left eye. He then saw the image so vaguely that he wondered whether the demonstrator told the truth about the structures he described—cell membranes, granular protoplasm, vacuoles, nuclei and nucleoli.

He could distinguish that there were separate cells, and he did see the nuclei. Nucleus! that was a new word to him; it seemed important, so he wrote it in his notebook. When he went home he added from his dictionary: "The essential part of a typical cell and the controlling centre of its activity." What a difference now! Yet it was the same microscope, and he did not feel changed. Wherein could the difference be? Study, lectures, demonstrations, practical classes, books—how had they altered him?

He remembered, early in first year, getting one or two books for each subject, and when he put them all together he felt that he had a library. He intended, starting with one, to read them all, so that he would know all they contained. Much later it occurred to him that if he learnt the contents of the books, he could dispense with them. His brain would have the information in it, and this would be his library. It was then that he first realized that some change must take place in his brain to hold knowledge as it was acquired.

The change that had taken place over the years and converted the raw, inexperienced student to the competent scientist, fully versed in his subject, had taken place gradually by diligent attention to his training and studies. In the course of these, he listened to lectures, saw demonstrations, read books and cogitated on all these matters, until his mind understood and was able to retain what he had learnt.

To acquire knowledge entails bringing information from outside to the mind and assimilating it therein. When a subject has been learnt, the mind is able to memorize it and retain it for future use. It is hardly conceivable for this to be the case unless the learning is associated with alteration of a more or less permanent nature within the brain itself. As neurons are the functional units of this organ, it seems reasonable to assume that this change would need to be located in the neuronic portion of the brain, and that for this purpose large numbers of neurons would be set aside.

The mind can receive impressions from the outside world only by the sense organs, which have therefore to be regarded as an integral part of the learning mechanism. In the sense organs, the first steps are taken that eventually lead to knowledge.

When a stimulus arising externally is received by an appropriate sense organ, it is transmitted centrally by the corresponding sensory nerve, and may, in certain circumstances, reach the conscious mind. On the way it passes by or through the sensory association area. This area could be the site where the impression is retained; that portion of the brain set aside for the neurons which are altered by impulses from the special senses. Those neurons actually altered by the impulse may be called impressed neurons, because the sensory stimulus causes in them a change which remains as a specific impression.

An impressed neuron may be defined as one that has been altered—more or less permanently—by the passage through it of a nerve impulse. The alteration is such that the characteristics of the nerve impulse are represented in it and retained in the neuron. A further inference is that an impulse passing through a neuron or neuronic arc, that has been impressed, will be altered by it to conform to the original impulse with which the arc was impressed. It is to be supposed, for reasons both of logic and of simplicity of function, that, having once been impressed, a neuron is no longer available for further impressions. New impulses have therefore to be directed to new, unimpressed neurons. If this theory is correct, then impressed neurons, in contradistinction to the cells of most tissues, are privileged to show their individuality by their function. Although impressed neurons may appear similar in structure, they differ according to the impression they retain.

It is as well to emphasize that similarity in structure and function of cells is no criterion that they are identical in make or action. The same impulse may pass through two neurons having the same appearance, yet be altered in character differently by each.

Two soldiers at a distance of half a mile are indistinguishable. At 300 yards, one is white, fat and short, the other yellow, thin and tall. At 20 paces, one speaks Swedish, the other Chinese. At two paces, one smells of rum, the other of spice. When shaking hands, one has hard, the other soft skin. It takes special investigation to learn that one spent most of his life at sea, while the other has never seen a large expanse of water. Much more is required before it is found that one has hypertension and the other diabetes.

The ability to study neurons must probably be rated at less than the half-mile standard, since it is not possible to study directly living neurons in the course of their activities. On this account, a group of impressed neurons is unlikely to show microscopic differences as an indication of their varied impressions. Inability to distinguish differences must not prevent admission of their possibility, but should stimulate research into the matter.

#### Structure and Function.

It is axiomatic that a close relationship exists between structure and function. Excellent examples of the truth of this abound throughout the body—gland cells with secretion and its collection, kidney cells and excretion, muscle cells and contraction, lung cells and gaseous interchange—but no better instance exists than nerve cells and conduction of nerve impulses. It is hardly believable that from an embryonic nerve cell, not more than a few microns in length, a nerve fibre several feet long can be developed.

The grouping of nerve fibres into bundles to form nerves, their insulation by a nerve sheath and the manner in which the nerves are dispersed throughout the body, make their function evident from structure and arrangement alone.

When specific structural changes have been developed to this extent, they simultaneously give the key to function; but, although all morphological modifications of tissue cells are purposeful, the connexion between structure and function is often very vague. Nevertheless, structure is subservient to function, and it must be carefully studied, particularly when the relationship is not evident and the function is poorly understood.

Good reasons have been given for considering mental activity as one of the functions of neurons; their structure will now therefore be considered.

#### The Structure of Nerve Cells.

A typical nerve cell or neuron is composed of a cell body and processes. The cell body is nucleated and has granulated protoplasm, some of which is grouped in collections known as Nissl's bodies. The cell processes consist of an axon at one end of the cell and one or more dendrons at the other end.

Although the functional unit of the nervous system is the neuron, it operates in collections or series, each neuron being physiologically connected with, though anatomically separated from, the adjoining neuron of the series by an area referred to as the synapse. The obvious nerve function of conduction of nerve impulse usually takes place in one direction only—"the law of forward direction". The impulse passes across the synapse from the axon of one neuron to the dendrons of the next, through its cell body and its axon via the synapse to the following neuron of the series.

Although an impulse passes over the whole length of the neuron and involves therefore synapse, dendron, cyton and axon, when the interval over which the neuron carries the impulse is great, it is by elongation of the axon that additional distance is accommodated. This seems to indicate that primarily the axon is the impulse carrier, and that any way in which the other components of the neuron differ from it must be for some purpose other than transmission of impulse alone.

The most striking differences between typical axons and dendrons are of length, number and branching. Dendrons are short, axons are long. Dendrons are multiple, axons single or very few in number. Dendrons branch repeatedly, axons rarely branch in this manner. The reason for the relatively greater length of axons has already been mentioned. The multiplicity of dendrons and their branches would allow impulses to be received from more than one neuron simultaneously.

The cyton, in contrast to ordinary body cells, is characterized by the presence of granular structures—the Nissl's bodies—which are therefore to be associated with the function of the neuron. That this is so is supported by the following facts. They diminish in number when a neuron is fatigued by use. They disintegrate when the functional activity of the cell is stopped or interfered with by the division of one of its processes. They are altered by certain poisons, febrile conditions and asphyxia, which upset the normal functional activity of the cell. It is generally considered that Nissl's bodies supply the energy transmitted along the nerve. Should this be the case, then they should also be capable of modifying an impulse being transmitted.

The structural appearance of a neuron, and the law of forward direction, are in keeping with the suggestion that in addition to transmission of nerve impulse, the neuron is able to modify it. It appears that different impulses arriving simultaneously at the cyton, through its dendrons, may be blended in it, perhaps with the aid of Nissl's bodies or similar protoplasmic substance. The modified composite impulse so formed is transmitted as a new impulse by the axon. The absence of Nissl's bodies from the axon hillock, although they are present in the basal region of the dendrons, is in keeping with this possibility.

The parts of a neuron, and their probable function, in physiological order, are as follows: (i) The synapse (functionally part of the neuronic arc) is the gateway to the neuron. It determines whether or not the impulse passes to the neuron, and possibly is the deciding factor in the type of impulse that may pass. (ii) The dendrons bear the impulse to the cyton. (iii) The cyton, including the base of the dendrons, but excluding the axon hillock, possibly strengthens the impulse. The cyton appears to be the most likely site where an impulse would be altered, and seems to be the region where impression is effected. (iv) The axon transmits the impulse from the cyton (axon hillock). The axon is probably not concerned in impulse change.

The neuron, as a whole, transmits nerve impulse with or without bringing about a change in its character.

The qualities of a nerve impulse leaving a neuron depend on the nature of the impulse before entering it, together with whatever alteration has taken place while it is passing through the cell.

From neuro-physiological studies, it is now known that a nerve impulse is a wave of electrical negativity. It travels through the axon without lessening in amount. The changes by which the impulse is transmitted take place in the substance of the structure through which it is passing. They appear to be ionic in character, but whether they are so or not, the important factor in postulating neuronic impression is that the impulse brings about a change of some sort in the structure of the neuron.

One may assume that, under similar conditions, the same impulse will bring about the same neuronic change, but if the impulse varies, then this variation will be reflected in the changes in the cell contending with it. If in some way these changes could be stabilized so that they remained, they would constitute a record having the characteristic variations of the original impulse mirrored in it. Subsequent impulses passing through this record would bear its variations and carry the same meaning.

#### Nerve Impulse.

The neuron is the functional unit of the nervous system, the tool by which the brain works. Nerve impulse is the form of energy used in doing this.

When a neuron responds to a suitable stimulus, electrical changes take place within it. When the electrical change proceeds along the neuron towards the brain, it is called an afferent or sensory impulse. If the impulse goes from the brain, it is known as an efferent or motor one.

After the passage of the impulse, the neuron returns to its original electrical state and is then able to respond to the next suitable stimulus.

Afferent impulses are divided into enteroceptive, proprioceptive and exteroceptive, according to whether the initiating stimulus arises from organs in the internal body generally, from muscles, tendons and joints, or from the external world.

A stimulus from the outside world does not excite an exteroceptive impulse directly; but has to pass through a sense organ. A sense organ is a structure interposed between the exteroceptive nerves and the external world. Its purpose is to convert the physical stimuli of light, sound and temperature, and others, to electrical impulses in the corresponding nerves.

Since exteroceptive stimuli are particularly concerned with keeping the mind in a state of awareness about the outside world, they are of the utmost importance in the development of the intellect and of the mind itself. Because exteroceptive stimuli are used in the formation of impressed neurons, the mind is formed to the tempo of the environment, and is therefore constructed to meet the varying conditions in which the individual will live. The mind is made from, and for, the environment.

Although exteroceptive impulses are of special importance in the study of psychiatry, this subject cannot be completely understood unless all impulses are included—proprioceptive, enteroceptive and efferent too. It is obvious to anyone that learning by means of exteroceptive impulses is intimately concerned with the intellect, because these impulses generally reach the conscious mind; but it is not so apparent that proprioceptive and enteroceptive impulses not normally rising to consciousness are vitally important to the central nervous system, of which intellect forms a part.

When one considers that all nerve impulses are electrical in nature, the similarity in exteroceptive, proprioceptive and enteroceptive impulses is at once apparent, and it must be allowed that these too can join with the exteroceptive impulses in developing the brain.

#### The Basis of Intellect.

The manner in which impressed neurons may be formed has been shown in the foregoing discussion; how they could be used to form the basis of intellectual functions has yet to be suggested.

One must assume that, for this important purpose, large numbers of specialized neurons are developed and held available for use, as required, by each of the exteroceptive pathways. These areas may be widely dispersed, but reason would place each group together and in close contact with their respective pathways. The separate collections need not then be together, but they would have to be neurologically connected and to function in close harmony. It seems likely that they would be located in the exteroceptive psychic and association areas of the cortex.

Whatever the location of these neurons, either they must be traversed directly by the exteroceptive impulse *en route* to the conscious mind, or the impulse may be divided, one portion going through the neurons, the other by-passing them to go straight to consciousness.

Once a neuron has been impressed by the impulse, a change takes place—possibly at the synapse—which renders it unavailable to future impressing stimuli, unless they are the same as that with which the neuron was impressed. When this is so, the entrance is facilitated. Restimulation by the repeated passages of the same stimulus deepens the impression, or alternatively, more than one neuronic arc may be impressed with the same impulse.

Subsequent impulses are directed to the next neurons ready to be impressed, and the process is constantly repeated throughout the life of the individual. In this manner, an ever-increasing number of neurons is impressed, forming a library in which all the significant exteroceptive impulses previously encountered by the individual are recorded. To this his conscious mind has constant access, and it forms the basis of his judgement when he is arriving at a decision or reacting to any situation, whatever it may be.

It is not apparent just how the mind reaches the arc containing the impression it requires, but somehow it is able to select the one it needs and to send an impulse through. The impulse is altered by the arc, in accordance with the impression that it holds. The altered impulse returns to the mind, where it is interpreted, and its similarity to the initial exteroceptive impulse, from which came the neuron impression, is recognized.

To carry out neuron impression, probably several factors are necessary. At least two of these can readily be recognized. The most important is the impressing impulse, which probably needs to be an exteroceptive one. The other point is that it rises to consciousness (of the conscious or subconscious mind). Other factors, such as the mood or emotion of the mind, or the significance of the impulse to the welfare of the individual, may aid in determining whether the neuron is deeply or lightly impressed.

#### *The Structure of an Impressed Neuron.*

For several reasons, it appears likely that Golgi type II neurons are the ones in which memory and other intellectual phenomena are stored. These neurons differ from the typical one, already described, in several important points. The axon does not leave the grey matter in which the cell is located, it does not form a nerve fibre, but rapidly branches into several ramifications. This departure from the structure of a typical neuron is appropriate when a minimal value is placed on the function of transmission of the impulse and a maximal value on its change or storage. The rapid and multiple division of the axon would allow the emerging impulse to be quickly carried away in several directions.

The construction of the Golgi type II neuron is admirably fitted to allow several different impulses to reach the cell at the same time, and for it to transmit the resulting compounded impulse simultaneously over many distinct arcs.

Structure, as has already been indicated, is very important in the understanding of how something works; but function too has to be studied. The correlation of both is needed to complete the full knowledge of a subject. One must therefore consider the functions that may be attributed to impressed neurons. This is best achieved by observing cases of psychological or psychiatric interest. It is proposed therefore to give the details of actual incidents and afterwards to comment briefly on their significance.

The missionary and his wife were killed, but their baby son, only a few months old, was spared and brought up by the Indians who had killed his parents. About ten years later the boy was found and removed from the tribe. He was educated and in due course received a medical degree. When he was over seventy years old he suffered a severe attack of pneumonia. In the course of his delirium he spoke the tribal language he had not used for sixty years.

A language completely forsaken rarely enters the conscious mind. The impressed neurons holding it are not therefore, as might be the case with ordinary memory, refreshed by intermittent use. This seems to indicate that once neurons are firmly impressed, the changes undergone may remain throughout the life of the individual. This being the case, unless a neuron can retain more than one impression when once in use, it can never be used for any other impression.

Since new impressions are made throughout life, there must be more than sufficient neurons available, to every normal individual, than he is likely to need.

The student took his dog out for exercise. The dog, elated by the prospect of a romp, rushed unheedingly on to the

road and was run over by a passing motor-car. From this the dog suffered a broken leg, which in due course mended and could be used without disability. However, it was a long time before the dog would cross the road again, and then only with caution and respect for traffic. Later, having lost this animal, the student replaced him with a puppy. Remembering the painful lesson to his previous dog—and thereby showing that some of his own neurons, as well as those of the dog, had been impressed at the accident—the student resolved to train the puppy. It took a long time, and many lessons, before the puppy developed the road sense that his predecessor had acquired in one. From the painful but rapid and the painless but slow education of his two animals, the student decided to profit still further. In so doing he was, without knowing it, making use of comparative psychology—a subject towards which modern psychiatry must turn more often as its importance becomes apparent.

The student realized that he had witnessed two methods of learning—one, that of repetition, involving a minimal amount of mental effort or concentration, the other, that of using a maximum mental concentration whereby it was unnecessary to repeat the subject more than a few times. He found the first method very suitable for learning requiring memory rather than understanding. In childhood, having learnt his alphabet and tables in this manner, he similarly repeated drug doses, a few each day, while walking to the hospital. He soon found that he began to retain them. The second method was better when the subject required concentration before it could be understood.

From these incidents, further information about the conditions influencing neuron impression may be gained. In each case the conscious mind has to be applied to, and is aware of, what is happening or has happened. The puppy at each lesson has to pay attention until he learns, remembers and obeys his master. The dog has to associate the road and the motor-car with the pain of the accident and the fear of a recurrence in similar circumstances.

The inference is that impressing is carried out by several contributing influences. By way of separate dendrons, more than one impulse can reach the neuron simultaneously and at the same time as the specific impressing impulse, or at a later period.

Alternatively, or in addition, the impressing may be accompanied by a linking up or association of the several relevant influences. In this case, an impulse from the mind would pass not only through the impressed neuron, but also through those associated. The depth of the impression and the importance in which it is regarded are increased by repetition, or in accordance with the significance of the associated factors.

The neuron impression of the puppy's mind and that of the student's mind are both to be considered as normal or psychological; but in that of the dog there is a suggestion of abnormality, and the condition may be regarded as psychiatric. The borderline between psychology and psychiatry is, in many instances, very ill defined. This indicates the interweaving of these subjects and the necessity for employing each in the study of the other. The significant difference, in the instances previously given, is that the dog's neurons were impressed in association with unknown terror. Numerous instances of this combination and its resulting abnormality (or is it after all a normal response?) are to be found amongst patients attending psychiatric clinics for the purpose of having the condition corrected. These patients can be cured of their condition when, by psychoanalysis or similar means, the whole incident can be unravelled and the association recognized; then with understanding the connexion between the incident and the unknown fear is broken.

#### *The Working of the Mind.*

During the course of his military training, the student's section was receiving instruction in the field on the transmission of messages by word of mouth. The trainees were placed at intervals around a large circle. The commanding officer, for reasons of interest or perhaps amusement, gave the student, the first member in the relay, the written message: "Aum man! padme hum." He read it out to the next man, and in due course the last one repeated to the officer: "How many of this party come?"

The student's cat was lame and weak in its front leg and its head turned a little to the side; consequently it was taken



to a veterinary surgeon. He examined the animal and reported the condition to be due to arthritis of the shoulder. Medicine was prescribed and given, but the cat's condition remained about the same. This veterinary surgeon's practice consisted mainly of large animal work, so when he was again consulted he referred the patient to a small animal practitioner of long standing and good repute. This one decided that the cat's condition was due to an infected ear and associated vestibular disturbance—a common feline disease, but rare in large animals. Treatment was altered accordingly, but still the cat grew worse. In desperation, a third opinion was obtained. Mainly on account of the duration of the history and failure to respond to previous treatment, an X-ray examination was advised. This disclosed the condition to be osteoarthritis of the cervical part of the spine.

Recently a psychologist asked a number of students to draw from memory the outline of a tree. From the type of sketch produced, he was able to detect significant facts about the mental power, character and general attitude to life of the individual responsible for the drawing.

Precisely how the brain works is still so far beyond comprehension that one must be very careful when making any assumption in the matter. If this is borne in mind, and if one keeps to generalities, it is allowable to make some suppositions as a working basis. It is fully evident that in the light of later knowledge drastic changes may be required, but, if progress is to be made, one has to start somewhere.

The diversity of material encompassed by the mind, and its ability to select immediately and at will whatever is required from it, make it reasonable to believe a system of classification, of the highest order, must be used to enable the mind to work smoothly or even to function at all.

Principles of classification require that like is grouped with like and that fresh material is not put in a new group, unless it cannot be worked into an existing one.

This assumption carries the implication that the mind is able to understand the material with which it is faced, or it could not know what to do with it. Should this be correct, then may it not indicate why psychological difficulties and psychiatric states are often associated with conditions beyond the comprehension of the mind?

The incident related about military tactics shows that, for reasons of simplicity and clear thinking, the brain prefers to make do with what it has, rather than to accept something new, unless this is clear-cut or associated with something of particular importance.

One can be certain that the brain cannot give out that which it does not have, and that any response relating to brain function has a definite basis in the brain itself. On this account, the foreign words, completely unknown by the men, became transposed by them to a sentence in their own language, which they could understand. In a like manner, the lame cat provoked different responses from different veterinarians. It is included here to show how the contents of one's "neuronic library" and the mental tendency to match current exteroceptive impulses with these may be a definite factor in differing medical opinions arising from one case.

The underlying basis in every case is impressed neurons and the manner in which they are incorporated in circuits. It is precisely for this reason that the psychologist was able to bring out the mental make-up of his subjects. It is instanced as a practical application of the same phenomena.

In accordance with the neuronic impressions a person has already made, he retains or rejects relevant features of a subject. These he is able to reproduce from memory, in the manner indicated. Because the brain classifies its material—impressed neurons—into groups, it is able to incorporate more readily that for which a group is already present than to start a new group afresh. It is therefore easier to learn more about something already known in part than to understand and remember something entirely new. As the field of accepted ideas enlarges, it becomes increasingly difficult to introduce new unrelated material. This is reflected in the comparative ease of learning in youth and the tardiness with which an old person takes in new ideas.

The qualifications of an old memory as against a recent one—its acceptance by the mental make-up, its additional significance by association with some important happening and the deepening of the impression by occasional recollection—are such that it is not surprising to find that memories of recent origin are lost in advance of those of longer standing.

Memories are recorded by the brain with much greater finesse than that based on similarity alone. The best recording systems incorporate time as an important aid to identification of the material handled. However, few systems do so with the accuracy, synchronization or attention to detail shown by the mind. From memory alone, it is possible to place an event as taking place a minute, an hour, a day, a year ago, or more, with a considerable degree of accuracy. Using hypnosis, as an aid in examining brain time recording, one may make a patient relive an incident with the time relationship of the various happenings completely in accord with those of the original affair. The visual, auditory, olfactory, tactile and other exteroceptive impulses placing the subject in contact with the occurrence are all recorded by neuronic impression in the exact time order with which they were received by the brain.

This seems to suggest that neuronic impression takes place at the time when the exteroceptive impulses are passing to the mind or immediately after their reception by it. It also gives support to the suggestion that neurons may be impressed with a compound impulse formed from the combination of all the exteroceptive impulses conjointly—a master impressed neuron. If this was so, the neurons set aside for impression might be located in one area of the brain, and not located in separate regions associated with the various sensory nerve tracts.

#### *Regression.*

Regression is the term applied to a state, created by hypnosis, in which the subject is apparently transposed in place and time to an earlier age in his life. The patient appears genuine in his responses and behaviour, and seems by his mental conduct really to be of the age to which he has been caused to regress. His responses give the impression that he knows and understands just what one would expect him to have known at the age or on the day indicated by the operator. In other words, his mind seems to have the same ideas, or the same impressed neuronic arcs are open to his subconscious mind, as was the case at that time. This may occur, even although when he is fully conscious and in the waking state he has no recollection of the events.

Both regression and the time coordination shown during the reliving of an occurrence support the inference that neurons set aside to receive impressions are used in order of their actual position, line by line and layer by layer.

The impressed neurons in actual use and the manner in which they are used (arcs and associations) are constantly changing, new neurons are added, old ones drop out of use, and the way in which they are connected is repeatedly being altered. Only in this way can the mind meet changing circumstances and keep up to date with the times.

So far the illustrations given are those of normal responses of a normal brain under ordinary circumstances. Various methods may be employed to bring forth memories unconscious in the normal waking state. As these somewhat alter mental activities, and thereby give, as it were, a view of brain functions from a slightly different angle than that normally seen, it is important to consider them so that the functions may be given perspective and a better judgement of them formed.

Chief among these techniques is hypnosis with its various phenomena—regression, reorientation, automatic writing, crystal gazing, and others—used with or without the aid of sedation. Psychoanalysis in the conscious or relaxed conscious states, as well as with light or deep sedation, may be used with both normal and psychiatric patients. The mental phenomena studied in these states yield useful information.



The following cases in which the patient was examined mainly in the hypnotic state will illustrate the point.

**CASE I.**—This patient, a young woman, complained of fear of spiders. Recently she had seen a large spider on the wall of her room. She immediately rushed from the room, felt weak and nauseated, had a vomiting attack and was prostrate for some hours afterwards. Under hypnosis she recounted an incident that had taken place when she was five years old. A spider had got into her auditory canal, and only with difficulty and after a period of time was it able to be removed. During this period the child was terrified both by the spider in her ear and by the panic that it caused to the grown-ups trying to help her. Explanation at hypnotic and conscious levels removed her subsequent fear of spiders.

**CASE II.**—A middle-aged woman had always been affected by smoke or fire. She was greatly disturbed by it, and could not rest until she had found its source and had seen that the fire was safely under control. One day she had a sudden attack of vomiting and collapsed in her bedroom. When examined, she was unable to account for this condition; but in the hypnotic state she quickly found that it had followed immediately after she had seen toast burning in an electric toaster with smoke billowing to the ceiling. Further investigation connected this incident with one that had taken place twenty years earlier, in which she had had a narrow escape from death in a bush fire. During this she had witnessed animals perishing in the flames, and her clothes were ablaze when finally she was rescued from the holocaust. On being awakened from the trance and told what she had related, she was astonished, for she had no conscious recollection of thinking about the bush fire when seeing the toast burning. After discussing and connecting the two incidents, she said that she felt differently about fires and lost the aversion to them.

Both these cases show how fresh material—new exteroceptive impulses—produces changes in brain tissue (that is, forms impressed neurons), and also how these changes are correlated by the mind with previously recorded incidents of a similar nature. Further, a comparatively trivial happening may in this way provoke a similar response to that produced by a catastrophic incident that has occurred many years previously and often without conscious connexion between the two incidents.

This suggests that the new afferent impulse, or its projection from the mind, continues through those already established arcs in which are placed previously recorded neuron impressions of a similar pattern to it. Its further course, particularly if there is no conscious distinction between the old and the new impression, is via the associated neuron connections previously made for the original. Finally, the impulse passes through the same efferent route and evokes the responses of the primary impulse. It seems impossible to conceive how this can occur without postulating permanent specific mental change.

**CASE III.**—A young woman, aged twenty-five years, was unable to drink hot tea without getting an attack of hiccups. In the conscious state she could offer no reason why this was so. Under hypnosis she remembered, when she was eleven years old, feeling very embarrassed at an afternoon tea party. She had always been afraid of her uncle, even though he tried to be nice to her. He spoke to her just as she was about to drink her tea, which was too hot to swallow; during her embarrassment hiccups resulted. On further investigation she revealed that the fear of her uncle was due to his having large, coarse hands. Still in the hypnotic state, she associated these with an incident that had occurred when she was seven years old. In this incident she was going to school with a companion, who ran away and left her alone with a man who accosted them. This man had similar hands to her uncle. The incidents and their connexions were explained to her, and her symptom vanished.

**CASE IV.**—A middle-aged woman complained that she was not able to work with an associate with whom her duties brought her in contact. The subject was able to believe no good of her co-worker, whom at first sight, before they had met, she knew to be a bad woman. A third colleague, who was on friendly terms with both parties, considered the subject unreasonable in her attitude and tried to bring the workers together. This she found to be impossible, since the subject put her own unfavourable construction on anything that her associate did, so that it further proved to her that she was correct in her contention. In the trance state, the subject related that when she was a child her

aunt had chased her with a hot iron and threatened to kill her. This was only one of the occasions on which her aunt had terrified her, and she regarded her aunt as a bad woman. On the day when she first saw her co-worker she was struck by the similarity with her aunt and subconsciously connected them. Explanation enabled her to overcome the feeling of fear and hatred sufficiently for the two women to work together; but the subject felt that she could never regard the other person as a friend or trust her.

Particulars of these two cases have been given to show how matters of everyday importance and interpersonal relationship may be dependent on impressed neurons and their association. Mistaken opinions and erroneous judgments may be formed and acted upon by an individual who may or may not be aware of the connexions used in the process. In a similar manner, neurotic physical symptoms can be formed. This is exemplified in the following two cases.

**CASE V.**—A married woman, aged thirty-six years, receiving treatment for nervous vomiting, remarked that she had developed excessive thirst and awakened repeatedly during the night with a dry throat. She slept with a jug beside the bed and consumed about two quarts of water per night, without quenching her thirst. In the course of hypnoanalysis she related how eighteen years previously, because she would not stop gossiping, her husband had thrown pepper into her mouth. Although this made her very thirsty, for fear of carrying the pepper further down and extending the burns, she was not allowed to drink. Her thirst and dry throat became very pronounced. Recently at her place of employment, the staff had become interested in a scandal, of which she took part in the discussion. She was informed of these particulars she had given, and the condition of her throat and her thirst returned to normal.

**CASE VI.**—(a) This subject was an intelligent woman holding a responsible position. She was forty years old, the mother of several adult children. At her work she was supervising the cleaning of an office when she suddenly became sick, vomited and developed a headache of the migraine type. For this she sought advice. In the waking state she could not account for her condition, nor did she know exactly when the headache commenced. When hypnotized she remembered one of the staff remarking how dirty the office was and how it smelt, adding also that one of her fellow workers often smelt strongly of perspiration. This reminded the subject of an event that had occurred fifteen years earlier when she was living outback, and one very hot afternoon an aboriginal lubra had entered her house. A gust of hot wind blew from the open window, and the odour from the lubra caused her to vomit.

The associations here disclosed were explained to her, in both the conscious and the hypnotic states, and she was told that her headache would not trouble her further. On awakening, she complained that her headache, although not so severe, was still present. She consequently was rehypnotized and a further history was obtained.

Two years before the office-cleaning episode she had visited her daughter—a trained nurse—in her quarters. It was a very hot afternoon and a hot breeze was blowing through the open window. She was considerably upset on noticing a strong smell of perspiration from her daughter. For two years the daughter bathed twice daily and took deodorants, but although the smell was not detectable to anyone else in the family the mother could still smell perspiration on her daughter. After this further incident had been explained to her the headache did not return, and since then the daughter no longer offends her mother as previously.

(b) The same patient noticed a persistent cough and dry throat, particularly when she was shut inside or at night during hot, windy, oppressive weather. This condition had been present for two days before she sought advice. Under hypnosis she connected these conditions with those encountered about twelve years previously when she was living in the Mallee. During dust storms in hot, windy weather, although the house was closed up, everyone developed cough and dry throat from inhaling the dust. Her symptoms disappeared after she understood the connexion between the two events she recounted.

It is apparent in the first incident that the daughter was innocent of offensive odour, but that the mother's mental impulses connected the two similar occasions, and passed over the arcs still holding the olfactory impressions made at the first and erroneously added them to the second impulses. In the same way, the coughing caused by reason of the dust on the first occasion was provoked by similar conditions, but without the dust, on the latter one.

The illustrations just given appear to be similar to those usually designated by the term *Gestalt* theory, in which certain configurations such as triangles, squares or circles viewed briefly in part appear to the observer as wholes.

Further examples of this tendency are to be found in the familiar pastime of seeing pictures in a fire or in the sky, and the greater ease with which a structure can be found if it is known—for example, when searching microscopically for a cell of a particular type.

The artist, no matter how faithfully he attempts to reproduce the scene before him, imparts characteristics to the canvas. These are so pronounced that an expert can readily decide whether or not a given picture could have been painted by a well-known artist. Similarly, the great masters of music implant their individuality on their work.

The implication from these examples is that the mind interprets exteroceptive stimuli in the light of previous exteroceptive impulses already stored in it. In other words, the impressed neurons and their associated neuron arcs can have an influence on neuron impressions formed after they have been established. This influence may, under certain circumstances, be sufficient to falsify subsequent exteroceptive perceptions.

A development from this, of considerable clinical importance in psychiatry, has been the evolution of mental function tests, one of which, the tree sketch test, has already been explained.

The ability of the brain to add something to that which is actually there, in order to make it fit into a structure previously known, can also allow it to omit details for the same purpose. One has only to visit a display of modern art to obtain definite evidence of both these capabilities.

What is true for visual exteroceptive perceptions holds for auditory and the other exteroceptive perceptions. The most likely explanation of why and how is that already given—namely, the necessity, when dealing with innumerable diverse impulses, of classifying them in some manner. For this to be practicable, similar impulses have to be placed together, and for simplification, if the impulses, though differing in some way, are sufficiently alike, then they are recorded as the same.

It is suggested that by a continuous repetition of the process previously described, the mind uses the exteroceptive impulses to build up a collection of impressed neurons in many ways similar to a library. The neurons impressed in this manner represent the knowledge acquired by the individual from which his actions, behaviour and mental responses are formed. On them, and in accordance with how they are associated, he is entirely dependent for his intellectual functions.

The importance of the earliest impressed neurons can hardly be over-estimated. Not only are they relatively few and must correspondingly take a greater share in mental responses, but they influence both the impression and the associations formed by neurons being impressed at later periods. Further, it appears likely that the manner in which early impressed neurons are incorporated into arcs or circuits may well set the pattern to be followed by subsequent impressed neurons. In this way they may determine the character of the individual.

It is incorrect to consider that neurotic impression does not commence until birth, as by that time sensory impulses have been in action for a considerable time, and it is even possible, as will be indicated later, that the scope of development may within certain limits have already been decided.

To use the analogy of the library, the main buildings, fixed structures and shelves are already present at birth. A number of important volumes may have been completed, and there is an almost unlimited number of blank books to be filled in during life. No new buildings can be erected, but some alteration of the working methods and rearrangement of the printed books will take place as the blank books are completed.

It is certain that from birth the neuron impressions are rapidly increased in number by the flood of visual and

auditory impulses which commences at this period. Intellectual processes, memory, reason, judgement, cannot arise until a basal sufficiency of impressed neurons has been formed. The individual's future responses throughout life are dependent on, and influenced by, the impressions held in these neurons. It is, therefore, vitally important that they should be suitable for this purpose. During this formative stage, the mind is in a state of flux and may be more readily altered than at any other time. Outside influences, particularly if harmful, are more likely to be effective at this than at any other stage of the individual's life. This period, from birth to two years, is one especially to be studied by the psychiatrist. Trends or disturbances at the earliest stages of development have greater influence than would be the case after stability of action has been reached.

Conscious memory, which necessitates recall of events, may be taken as an indication of neuron impressions at the time of the event recalled. In the adult, it usually does not extend back further than the age of about three years, by when much of the character of an individual may already be indicated. If character is dependent on neuron impression, as well as on other factors, then one would expect earlier indication of impressed neurons than those formed at about the age of three years. Evidence that this is the case can be obtained from suitable subjects in the trance state. Reports are available of memories dating from the first year of life. In one case, improvement in the patient's condition followed their recall.

Some workers hold that by means of regression in the trance state it is possible to secure memories of the neonatal state. To the foregoing contentions strong support is given by the two following cases; both the patients are somnambulists and were examined in the deep trance state.

CASE VII.—The patient, a woman, aged thirty-seven years, complained of headache of the migraine type. She was caused to regress to the first headache she could recall and instructed to remember the details. When she was brought again to her normal age she was able to recount how her elder sister, left to mind her, tumbled her head over heels several times on a bed. This brought on headache and pain in the back of her neck. The incident occurred before she could walk, and she gave good reasons to support her age as being then eight months.

CASE VIII.—The patient, a woman, aged twenty-six years, was instructed to regress to her earliest memory. On waking, she described how she remembered lying in her perambulator watching her mother making cakes. She could not say what her age would have been, but knew that it was less than twelve months. It was before she could walk.

The next two cases are included here to show that not only memory but also mental responses characteristic of the adult may have their origin at a very early age.

CASE IX.—A female patient, aged thirty-five years, was suffering from *anorexia nervosa*. In a deep trance state she was asked to recall the first time she could remember vomiting in the manner she now knew to be typical of her condition. She was able to tell with extraordinary detail of an illness which had commenced when she was aged two years and three months. In it she was jaundiced, vomited frequently and was carried about her parents' farm in a clothes basket. She knew that no one expected her to live. In later life she vomited when subject to stress such as fear, worry, fright et cetera.

CASE X.—The patient was a female, aged twenty-six years, who very occasionally had vomiting attacks. Hypnoanalysis disclosed her earliest remembered vomiting bout to have occurred when she was aged two years and five months. She was to go to her first party, and her mother stood her on the table to put the final touches to her dress, a somewhat stiff yellow organdie party frock. The frock stood out at a wide angle to her body and disclosed most of her legs. She knew that her legs were thin, and anticipated unfavourable comment from the other children at the gathering. She promptly vomited on her frock, because she knew that this would prevent her from going to the party.

If the theory postulating neuron change resulting from incoming stimuli, the retention of so-formed neuron records and their use as a basis of mental acts is accepted, then the reason for various commonly encountered behaviour traits becomes apparent. No two individuals

can have the same neuronic records, and contradictory opinions may therefore be given by different individuals on the same matter. Even those expressing the same opinion will have varying shades of reason by which they reach their conclusions. Herein lies the explanation for individual argument and industrial and other disputes, as well as international disturbances.

For reasons of survival, it is essential for an individual to react to the best of his ability in a given situation. One tends, therefore, to decide and act to the best of one's judgement, even though one may be ignorant of essential details. It is for this reason that every individual feels that his own conclusions are the right ones, and the spectacle of an expert or prominent citizen making foolish statements on matters outside his province may frequently be encountered.

#### Heredity.

The changes resulting in the production of impressed neurons so far considered have been due to environmental factors. It may also be possible for neuronic impressions to arise from hereditary influences—that is, for some neurons to reach maturity and be changed so that they function in the same manner as neurons impressed through environmental means, the change being brought about as the completion of hereditary influences.

Such an hereditary neuronic change could account for instinctive behaviour, when an animal reacts in a pre-determined manner although it is meeting the situation for the first time. The reaction is similarly exhibited by all members of the same species. Whether neurons are impressed under hereditary influence or not, there can be little doubt that it plays a very important part in mental activities.

Although heredity is generally considered in relation to the present or to comparatively recent times, hereditary influences may be traced back over vast eras. It is important to realize that in the process of evolution of a species, hereditary influences are acquired or lost throughout the period. These influences are inherent in the fertilized ovum, and control the development of the individual as it runs its evolutionary course from fertilization to maturity.

The theory of evolution postulates that by a gradual process of modification all existing life has developed from a single-celled organism. This process has been existent for some hundreds of millions of years. By the trial and error method, combined with the survival of those forms whom the change has better fitted to withstand the hazards of environment, all living individuals now existing have arisen. In some manner, Nature has endowed the individual with the ability to retain the change and to transmit it through the germ cells. To the phenomena whereby parents are able to transmit characteristics to their offspring, the term heredity is applied.

To understand heredity and to benefit from this knowledge, it is even more necessary to study the course of its development from the primitive ancestral unicellular organism to the multicellular flora and fauna at present in existence than to apply the mind diligently to genetics—animal and plant breeding, Mendel's laws, chromosomes, genes or other manifestations of heredity at its present stage of development. By the latter procedure is shown a cross-section of its evolution; by the former is revealed the way in which that period has been reached. If the inheritance of the cell results from changes in the past, how can these be observed in the present?

There are two important avenues by which this can be done—namely, by comparative studies of existing species and by embryology. Both were used by Darwin in arriving at his theory.

During the course of evolution, the older forms and the new arising from them continue to exist together and conjointly compete for survival. There can be found at present a sufficient variety of specimens, representing the various stages of development, to enable the path followed by evolution to be traced back to the primordial cell. By the comparative study of the different members of the whole animal and vegetable kingdom, the significance of

both structural and functional evolutionary changes may be determined.

Modern psychiatry owes a great deal to evolutionary study, and will come closer to it in the course of its development in the future.

The whole trend of evolutionary change is such that the individual improves his ability to respond to his environment. By corollary, characteristics remaining unchanged for long periods are of the greatest importance; if not, they would have been discarded for something of more value. The further back along the evolutionary line a structure or function can be distinguished, the more basal it must be to the needs of the individual. Special attention should therefore be given to characteristics found in species both of recent and of remote evolutionary development. Such a course was followed by Cajal, and it enabled him to point out that the neuronic arc, during its evolutionary development, has passed through the following five great epochs: (i) the epoch of irritability, involving two adjoining cells, one receptor and the other effector; (ii) the epoch of the reflex arc, in which the receptor cell has divided processes and makes contact with more than one effector cell; (iii) the epoch of the intersegmental reflex neuron, in which an additional neuron is interposed between the receptor and effector cells; (iv) the epoch of the suprasegmental reflex neuron, in which additional new nerve elements are placed between the receptor and the effector neurons; (v) the epoch of the psycho-associational neuron, in which psycho-associational neurons are added.

A sixth epoch not included by Cajal, who was concerned with the reflex arc, can be added—namely, the epoch of the unicellular organism, in which the unicellular organism acts as both receptor and effector.

From a consideration of these six epochs a law may be formulated—the law of "response to a stimulus" or the law of the "maintenance of *status quo*".

It is characteristic of living matter that it responds to a stimulus, and that, having responded, the organism tends to return to the resting stage, a state of balance in which it is best able to respond to the contingencies of a varying environment. This characteristic has been present throughout the entire period of evolutionary development and is vital to living tissue.

The unicellular organism, necessarily, itself responds to a stimulus it receives; but the multicellular organisms concerned in the five later epochs have cells differentiated into receptor and effector functions. In the earlier epochs—that of irritability, the reflex arc and the intersegmental reflex neuron—the receptor-effector connexion is strikingly apparent, because the effector response occurs immediately and is the obvious result of the stimulus applied to the receptor.

The epochs of the suprasegmental and the psycho-associational neurons have been achieved only by the addition of innumerable internuncial neurons made necessary for the purpose of extending old and developing new functions in the nervous system, the ultimate outcome of these additions being the development of mental activity as encountered in the mammalian mind. One ensuing result of this enormous increase in the number of neurons comprising an arc is the appearance of inhibition or delayed response. Another obvious outcome is that the path taken by the impulse may be so hidden by the number of possibilities open to it that it is difficult to determine which effector response has resulted from which receptor impulse.

For these two reasons it is no longer apparent that there is a connexion between afferent and efferent impulses, and the various manifestations of higher mental activity are apt to be considered as isolated entities—at least in so far as afferent and efferent impulses are concerned. Nevertheless, the law of return to *status quo* holds, and when a receptor receives a stimulus, the impulse must be passed on to the next neuron before the receptor can be cleared from the effects of carrying the impulse. It is then ready again should a later stimulus arise. The impulse continues along the internuncial neurons through which its path is



directed, and they in turn pass on the impulse before returning to the normal resting stage. Finally, by contact with the effector neuron, the impulse satisfactorily completes its course, and the whole of the complex arc involved becomes available for use when next required.

In this way, the later epochs comply with the characteristic behaviour that is a prominent feature of the earlier epochs. Indeed, this necessarily follows, since the later arcs are developed from and must conform to the pattern of behaviour of the earlier ones.

An analogy will be given to show the similarity between the creativeness of the human mind and the method of evolution exhibited by Nature. It will serve to explain how both become involved in difficulties, and why some psychiatric conditions have arisen during the course of mental evolution.

The student, now a practitioner of many years' standing, found himself in the position of being able to afford a new motor-car. He consequently purchased a most attractive model, one in which for the first time the gear change lever had been moved from the floor to the steering column. This alteration gave much more front seat room and was considered a great improvement over the older models. The car was not long in use, however, before mechanical faults developed in the gear change mechanism, and it was always giving trouble.

It frequently follows that, when a new advance is made, in the early period of its application faults develop. With further time, experience and experiment, these are overcome; but until this period has passed and the advance consolidated into a reliable gain, troubles are apt to arise.

To revert to Cajal's epochs, the two last-mentioned of which depart somewhat from their predecessors in that the addition of numerous internuncial neurons allows inhibition of the impulse to take place; this is to enable the individual so developed to have certain advantages over those whose less complex nervous system of the early epoch types causes an immediate reaction to a stimulus received.

In relation to the period of time over which the nervous system has developed from a unicellular response to the present, the age of the two later epochs is very little. Considering the vastly greater complexity of the later developed neuronic arcs, there has hardly yet been time for faultless performance to have emerged. The relatively recently developed storage or inhibition of an impulse is contrary to the older and firmly established immediate response to a stimulus. It is to be expected, then, that difficulties associated with the functioning of the more recently developed neuronic arcs are to be encountered.

### Neuroses.

It is quite possible that the difficulties in mental activity, mental energy and ability present in individuals may depend on the manner in which these neuronic arcs are built up. If the incoming impulses are dissipated over too many paths or fail to reach proper effector neurons, then the mental responses will be abnormal or weak and the individual less competent than one with properly connected neuronic arcs. Many of the neuroses which form a large part of psychiatric practice may arise from this cause. The patient (Case IX) affected with *anorexia nervosa* may be considered to show how this could take place.

It has been firmly established that, once an impulse has passed over an arc, subsequent passages are facilitated, and it is considered that by this means pathways are set up. The more frequently an established pathway is used, the easier it seems to be for an impulse to use it, and the greater its importance becomes.

When the *anorexia nervosa* patient was a child, she had infectious hepatitis with symptoms of persistent alimentary upset—vomiting and diarrhoea. Thus, at the early age of two years and three months, an important effector pathway was used greatly in excess of normal limits and made exceptional associations. Any afferent impulses not carefully guided through the internuncial neuronic maze

by established routes may have come at first by chance, but later by precedent, to use this prominent effector outlet, which terminated in vomiting and diarrhoea. Subsequent incidents in this patient's history seem to show that this course was followed, and the chain of events indicates that there was a neuronic association connecting vomiting and diarrhoea first with fear of death, later with fear and severe shock, and ultimately with minor mental upsets such as anxiety, worry, minor shocks and slights, until by the age of twenty years nervous vomiting attacks frequently occurred.

As yet it does not seem to have been clearly specified which effector responses may come to produce physical symptoms in this manner; but afferent impulses constantly pouring into the brain cannot simply be stored there—eventually they have to be balanced by efferent impulses, and the sequelæ they set in motion. Symptoms which commonly seem to arise in this manner include the following: vomiting, diarrhoea, palpitation, vascular changes (blushing), dermatitis, sweating, trembling, asthma, hypertension, talking, eating, drinking, alcoholism and glandular secretion.

One of the most important contributions made by modern psychiatry to medicine and surgery is the recognition of the mental origin of many signs and symptoms previously considered as characteristic of organic physical disease.

Diagnostic difficulties, encountered in deciding whether a symptom has a functional or organic basis or both, are very real.

The generally accepted method of looking for organic changes and attributing the cause to these if they are found, is not good enough. Modern psychiatry is showing how frequently a mental background may be the sole cause or may be acting in addition to physical abnormality. Much more attention is being given to this group of disorders, and hypnosis is a very useful diagnostic aid in these cases (see the cases described). A particularly good example is the case of *anorexia nervosa*. This patient, on separate occasions, underwent an appendectomy and a cholecystectomy. Her operations may have been necessary; but any patient with recurrent abdominal pain and vomiting may easily lose a normal appendix and gall-bladder.

CASE XI.—In the following case, a man, aged forty years, suffered from a severe anxiety state sufficient to prevent him from working; this followed the death of his wife, of whom he was extremely fond, and for whose death he felt himself partly responsible. He was treated by hypnoanalysis, during which he recalled the incident of his wife's death in detail. After this he improved considerably, and for more than two years has been able to enjoy his work. For a period during his recovery his previous symptoms disappeared, but were replaced by periodic attacks of diarrhoea with colic. These were fully investigated in a public hospital and reported as being nervous in origin—no organic basis could be found. In most instances, with the aid of hypnosis, it was possible to relate each attack of diarrhoea with a mental factor occurring a few minutes or hours beforehand.

CASE XII.—Another male patient, aged forty-five years, had been the subject of severe migraine at frequent intervals since childhood. It was suggested to him that attacks often followed immediately after incidents associated with mental conflict. Later, the subject was able to correlate at their onset two attacks, recognized by premonitory symptoms, with mental worry. Neither attack progressed further, and since then no fresh headaches have appeared, although the period of time greatly exceeds any previous interval that he has experienced between attacks. Since then he has been subject to outbreaks of dermatitis, a condition frequently occurring in his brother.

If these two cases are significant, they might be explained by concluding that the blocking of one efferent pathway was followed by the establishment of a fresh one.

Perhaps the most common of the neuroses is the anxiety state, a condition often present without causing sufficient distress to compel the subject to seek advice. This condition is one of both fear and uncertainty. It parallels the usual response of a normal individual to sudden danger, but differs in the persistence of the response when no danger exists.



In anxiety neurosis there appears to be an imbalance of the normal effector pathways, in which improper and excessive use is made of those rightfully employed in response to danger. Such a condition may arise through abnormal exposure to danger stimuli early in the development of the mind, before those effector pathways normal to the individual have been consolidated. In this way an individual may almost constantly be reacting to non-existent danger, while nerve energy, which should be spent in useful effector responses, is wasted.

In the discussion of impressed neurons and their association or the connexion made through their dendrons and axons, it was pointed out that among the factors concerned, two were of particular importance: one the sensory impulse, which gives specific characteristics, and the other a state of awareness and understanding by the conscious or subconscious mind, whose influence, partly at least, governs the classification of the impressed neuron and directs its associational linkage.

It is evident that the mind cannot carry out this fundamental linkage without both knowledge and appreciation of the significance to the individual of the incident evoking the afferent stimulus.

In everyday life the conditions under which the mind may need to respond quickly or the individual will suffer, and of which time for appreciation is not available, are those of sudden crisis—terror, fear, panic. The individual answers these stimuli by the danger response with the addition of any other well-used pathway—for example, vomiting or diarrhoea—particularly if these are excessively developed. The mind in these cases acts without awareness, and the impressed neurons recording the incident cannot be classified and associated with their proper connexions. They remain out of place, but marked in red: "Don't stop to handle! Apply danger response immediately." When this state of affairs persists, subsequent events, in some way recognized by the subconscious mind as being related, are hurried through the same neuronics, arcs and discharged by the same effector responses as the original stimulus.

Reasons of survival require immediate response to danger and anything the individual associates with it. In such circumstances action may be needed before consideration; delay may mean disaster. Incidents of this kind are of paramount importance and leave outstanding mental effects. This enables the recognition of the associated and possibly trivial events to be readily made in the hypnotic state.

Several of the cases earlier described illustrate the point mentioned. Case II will serve to show it in more detail. In this case the initial cause of the danger response was being trapped in a bush fire and the terror brought about by it. Twenty years later a harmless incident without conscious connexion produced a similar response. It is interesting to note that, in addition to the usual response to danger, this patient reacted through the efferent pathways that lead to vomiting. This is very important, for it indicates that physical symptoms may arise from mental abnormalities. The symptoms shown depend upon which efferent pathway is dominant for the individual. Thus one patient may respond by vomiting, another by diarrhoea (Case XI), a third by both. It appears not unlikely that other symptoms, such as excessive urination, tachycardia, asthma, dermatitis, can arise similarly from innocent origins quite outside the patient's conscious knowledge.

A further example of this kind appears to be afforded by the action of recurrent stress. Selye's work has shown that continued mental stress stimulates the adrenal and pituitary glands excessively and ultimately results in physical change. The connexion between the mental and physical aspects of this syndrome can best be explained as a disturbance of the normal afferent-efferent impulse relationship in a similar manner to that already shown.

In the normal individual, when the danger period has passed, the incident producing it is carefully recalled and analysed by the conscious mind. When the analysis is complete and the mind is aware of the significance of the

event to the individual, it can be classified. It thenceforth ceases to produce the danger response, because the neurons in which it has been impressed are associated to their correct arcs.

Under exceptional circumstances, or with certain types of mentality, the conscious mind cannot recall or satisfactorily analyse the danger incident, and it remains as a resistance. In these cases the connexions between the conscious mind and the relevant impressed neurons are closed. The incident cannot be remembered until the way is opened.

Under certain conditions the mind may be assisted to overcome a resistance and recall the details of its origin. When this is possible and the information is accepted by the conscious mind, the resistance is permanently removed, together with the symptoms it had previously produced.

Amongst the methods which assist in breaking down resistance are discussion, confession and association. When the influence is strong, Freud's methods of psychoanalysis, including free association and the use of sedatives, may yield more satisfactory progress.

In suitable subjects hypnosis is a powerful agent which may enable events, otherwise excluded, to be recalled and later evaluated by the conscious mind.

One of the most outstanding contributions to the knowledge of mental function has been the work of Pavlov. His discovery of conditioned reflexes opened a new era in the understanding of behaviour. The readiness with which conditioned reflex action is to be explained by the impressed neuronics and effector-effector impulse theories is further evidence in support of these.

During natural development an animal establishes food reflexes. The sensory food stimuli—smell, sight and taste—are transmitted centrally, where they are recorded permanently by neurons appropriately changed. These impressed neurons then become part of the arc through which future similar impulses pass. The further course of the impulse is by the effector pathway resulting in the actions, such as salivation, needed in dealing with the food.

The sensory stimuli, by which conditioning is instituted, such as the auditory impulses of a bell, form their own impressed neurons, which are then connected to those bearing food impressions. After this route has become established, auditory impulses from the bell pass through the neurons, matching them to the food-impressed neurons and, following their connexions, call forth the same effector response.

The similarity between this course of events and those exhibited in Cases I, II, III and IV is both definite and significant. It serves to show how readily a natural response may be influenced to produce pathological effects, and indicates the close relationship of psychology and psychiatry.

Copying what one sees someone else do and following instructions given are two very important methods of learning; both have as their underlying foundation sensory impulses, impressed neurons and usually their evaluation by the conscious mind. Examples can readily be found to show their effect on behaviour. A few will be given.

When two individuals live in close association for a number of years, they tend to develop the same characteristics of behaviour. In most instances this may be regarded as a normal reaction; but when one completely dominates the other, it is considered to be an abnormal condition and is designated by a special name, "*folie à deux*". The tendency to implant characteristic behaviour features is a related condition normally regarded and frequently encountered in veterinary practice. Veterinarians know that dogs often mirror their owners in behaviour; that groups of cows belonging to one owner may be excessively timid and shy, while other herds are placid and unafraid.

An interesting case reported in a human subject is that of an American baby brought up by Chinese. When the subject was an adult, the mannerisms and responses were

such that, except for his fair hair and blue eyes, the man would have passed for a Chinese.

In view of the tendency of an individual to conform to the behaviour of those with whom he is closely associated, a patient, a middle-aged woman with an anxiety neurosis, was placed at work with two men of placid temperament. It was reasoned that there would be less likelihood that the normal behaviour of the two men would be materially altered than that the abnormal responses of the patient would be. Further protection was given to them in that there were two against one. The work done was such that some required the combined effort of two or even the three to do it, while some could be done individually. Six months later, the patient reported a great improvement—but not cure—of her condition, and further gain was evident at the end of two years more.

One case by itself is not significant and in two years adjustment might have occurred under any ordinary circumstance. The patient was therefore questioned as to what she had learnt, and asked if she could explain why she felt so much better. In the waking state she was unable to give a satisfactory answer; but assisted by hypnosis she gave her reply very definitely. By watching her two companions she had noticed that they worked deliberately and kept their attention on whatever they were doing. She therefore came to work more slowly and concentrated her mind on the task as she was doing it.

This suggests that for work requiring mental concentration the sensory impulses arising from it are ultimately directed to those efferent pathways initiating the movements necessary to carry out the task. This produces the normal balance of afferent and efferent stimuli which is required by the brain for proper function, free from abnormality. The greater the length of time occupied by the brain in this way, the less the opportunity for conditions resulting from abnormal responses to develop.

If the balance of impulses theory is correct, then study directed to the period when the efferent and afferent pathways are being developed is vital to psychiatry.

Knowledge of conditions influencing development of these pathways might well result in allowing prevention of much mental illness, which when once present, may already have passed the possibility of cure and be able to be treated by palliative means only. With additional knowledge of this nature it may then be possible to devise means of assisting normal development of the mind, as well as protecting it from deleterious influences during the critical period of its development.

The methods of treatment found by experience to be best suited to use for the anxiety neurosis are, briefly, rest, adequate sedation, reassurance and abreaction. These may effect a "cure" in acute cases (for example, shell shock) in a few days, if promptly used.

The success of this treatment supports the balance of impulses and the impressed neuron theory. Rest and sedation limit the pressure on incoming impulses, reassurance and abreaction assist the correct associations and the proper outgoing pathways to be selected.

If mental concentration assists in correctly balancing the affecter-effector impulses, it is at once apparent why patients with anxiety neurosis derive benefit from purposeful pastimes, competitive sport, occupational therapy and other means whereby strict mental attention is compelled. For the same reason, monotonous work which soon comes to be done in a reflex manner dissociates the mind from the individual's occupation and indirectly disrupts the balance of the affecter-effector impulses.

The present age has, with good reason, been called the machine age. Mechanization is advantageous if machines are working in place of men; but when a man becomes little more than an indispensable cog and works for the machine, an unnatural environment is created for him. Many of the occupations at present followed lead to the type of work in which mental concentration becomes unnecessary. This is practically the case in factory work.

Research by Dr. Russell Frazer into the incidence of neurosis in factory employees showed that neurotic illness

caused one-quarter to one-third of absenteeism due to illness, 10% of the total employees were afflicted with definite and disabling neurotic conditions, and a further 20% had minor forms of neurosis.

Various surveys place the incidence of psychoneurotic illness amongst the general population at somewhere between 0.8% and 1.1%. The enormous increase found among factory workers strongly suggests the influence that this type of work has on the individual, and gives added support to the theory put forward for the cause of anxiety states.

If this is correct, then means of dealing with the problem can readily be formulated in conformity with psychological principles based on the theory. The role of the psychiatrist in outlining the principles in clear, definite terms is obvious. The importance of identifying workers best suited mentally to withstand the consequences of factory work, and the need for early recognition and treatment of abnormality when symptoms do arise, are duties that can be satisfactorily performed only by a psychiatrist.

The incidence of neurotic illness in the general population appears to be increasing rapidly and at a greater rate than could be accounted for by its increase among factory workers and the growth in numbers of those so employed. Two factors may well be operating to produce this result, both arising from the tendency to submerge the individual in groups of similar individuals. One is that workers are paid fixed rates according to the type of work done, rather than by the manner in which it is performed. This provokes loss of interest in the work and reduces concentration on it. The other factor is the development of the "Welfare State". Both these factors result in the "don't care" complex; it becomes a right to receive something for nothing, and the honest worker becomes an object of ridicule and scorn. Both these factors ultimately tend to disrupt the individual's mind by interference with the normal functioning of the affecter-effector pathway balance. Both may be combated and mental health safeguarded if the value of concentrating on what is being done is given recognition.

#### The Development of the Mind.

It has been suggested that the collection of impressed neurons forms the basis of intellect and behaviour, and that disturbance of the affecter-effector impulse balance, in which arcs of impressed neurons are somewhere incorporated, may lead to mental illness of the anxiety type. Reasons based largely on neurological principles and facts have enabled this theory to be set out in detail; but in the process reference was made to the conscious and subconscious mind, and in particular to the state recognized in them as awareness and understanding.

The manner in which the mind attains this state is still beyond comprehension, but some pertinent remarks will be made after an allegory has been given by way of illustration.

The practitioner badly needed a holiday with complete freedom from interruption by professional matters. He therefore would not disclose his destination, but admitted that he had a special reason for choosing it. In due course he left his home in Bendigo. His family, with natural interest and curiosity, busied themselves with speculation. At first nobody knew in which direction he had gone, or even what could be the reason for his choice of destination; but when his letters started to arrive from Albury, Canberra, then Sydney, they knew the route over which he had passed. From it could be determined not only the direction his later route would take, but also where it would not be. Later it passed through Brisbane, Townsville and Cairns. His family found that the further he progressed along the way the more precisely could his future course be plotted. It was not until his return that they learnt that the purpose of his trip was to see the Barrier Reef at Green Island.

The development of the mind may be likened to this journey. In each, at the start, the direction was unknown and the purpose undisclosed. Each has provoked speculation as to how, where and why. Because the mind is still developing, one cannot tell where its ultimate goal will be or what its final state. However, it has proceeded

a long way on its course, and clearly shows the direction taken in the early stages.

It is thus possible to say that each new stage of development brought about an improvement in the ability of the individual to compete satisfactorily in the struggle for existence. Each advance has been effected through the modification of and addition to that already existing.

The journey of mental development has been mapped out by the study of evolution, to which reference was made earlier. Since all higher forms of life have come from unicellular organisms, they are to be regarded as the starting point and to be compared with Bendigo in the physician's journey. How far relatively the journey of mental evolution has progressed from this point it is not possible to determine, for the end of the road is not apparent; but a sufficient distance has been covered to enable certain definite tendencies to be apparent in which development takes place.

The first of these is that each new improvement is possible only by virtue of that already gained, just as the practitioner could reach Sydney only because he had passed along the previous route. Similarly, by the time the practitioner had reached Brisbane, the general direction of his journey was fixed, and his relatives knew that he would not suddenly be in Perth; so it is even less possible for mental development to appear in a totally different form, quite unconnected with its previous manifestation.

From the standpoint of evolution, the more advanced the brain, the greater the complexities of both its structure and function. So far, the peak of mental development is that achieved by man, whose mind is so complicated that it is difficult to conceive its nature or to understand the process of its action. In spite of this, the human brain is but the product of much simpler structures, more capable of explanation.

There is, therefore, good reason to study these carefully, so that the more complicated structures developed from them can be more readily understood.

The critical point in mental evolution is that where delay in response to a stimulus first occurs. It is here that the mind, based on understanding, commences to diverge from the mind, if it can so be called, based on instinct.

Both the conscious and subconscious minds may have arisen at a later period than any of Cajal's neuronic arc epochs. However, it is by means of these arcs that the complex mind has been evolved, and the closer study of them may yet lead the way to better understanding of the higher mental functions.

Although one cannot yet determine how the brain reaches awareness and is able to perceive meaning, that it can do so is a necessary consequence of evolution.

It could be that there has been some completely new development, of the nature of which so far no good lead has been given; but this appears unlikely. A much more probable explanation is that a still higher arc—the seventh of the series—may have been evolved. It may include afferent and efferent thoughts which would need to follow one another in a routine similar to the afferent-efferent impulse sequence previously described.

Possibly the Eastern races, with their different conceptions of the mind, may have some important contributions to make to the better understanding of thoughts, ideas, will-power and other mental phenomena.

Medical practitioners cannot fail to notice the wide variation shown by different patients in their mental outlook and its influence on the course of their illness. One subject may succumb to a minor complaint, while another may withstand grave conditions in which the physical signs suggest a hopeless prognosis. An extreme example of the effect of mind over body is shown by the "bone pointing" of aborigines, in which a native may be willed to death. Bader, the British airman who lost both his legs in an air accident, but went on, first to defeat his surgical handicaps, and later to surmount physical disabilities, showed mental tenacity almost beyond comprehension.

Antarctic and Arctic travel abounds with instances in which achievement and often survival have resulted largely from will-power—the ability of the mind to drive the physical body. Nansen's experiences as described in "Farthest North", Douglas Mawson's "Antarctic Ordeal", and "The Worst Journey in the World", by Cherry Garrard, are outstanding instances showing the amazing extent of the physical reserve which mental drive can call forth from a healthy physique.

Along these lines an observation of Spencer Chapman is of particular interest. He reported that individual soldiers isolated in the Malayan jungle by the Japanese advance almost invariably perished. The length of time of their survival varied in accordance with the intelligence of the individual. The majority of private soldiers lasted about a fortnight, but officers were able to live for up to about six months. Chapman attributes the difference mainly to the greater will to live of those better developed mentally.

The patient's mental outlook on his illness is an important factor in response to treatment. Modern psychiatry is a valuable aid to both medicine and surgery, by assisting the patient to regard his condition favourably.

Apart from the connexion between mental outlook and response by physical means, there is another group of physical conditions in which mind and bodily alteration or abnormality are joined. This group has attracted considerable attention in recent years, and its importance is rapidly increasing. In recognition of the role these conditions play in medicine and psychiatry, they have been classed together under the name of psychosomatic medicine.

Psychosomatic medicine refers to the relationship by which mental, particularly emotional, disturbances result in changes of bodily structure and function, and of the effect produced on the mind by bodily abnormalities. Numerous instances of these conditions are commonly encountered, such as palpitation, blushing, sweating. The sympathetic and parasympathetic nervous systems and the endocrine glands are frequently incorporated in these responses. In its widest sense psychosomatic medicine is involved in all medical and surgical conditions, for even nephritis or a cut finger has some effect on the mind, and so has an emotional influence.

This development of psychiatry has brought it much closer to both medicine and surgery, for many of the conditions now coming to be recognized as of mental origin were previously considered as being strictly confined to organic physical change. One important result of the study of this subject is to emphasize the need to treat a patient as a whole individual, and not as a collection of separate abnormalities. In this respect, medicine, surgery and psychiatry collaborate conjointly to benefit the patient in his entirety. While each illness carries some mental effect, and this should always be considered, it is to a special group of conditions that the term psychosomatic medicine is generally applied. Members of this group include peptic ulcer, colitis, rheumatoid arthritis, high blood pressure, asthma, migraine and others.

It is amongst this group that the work of Selye on stress and its effects is to be found. This important study has been mentioned earlier, and the explanation has been given—namely, that impressed neurons and their associations come to lead stress impulses into the efferent pathway of glandular response. It is interesting to note that endocrine secretion may be influenced by purely mental factors. Physiologists have for a long time regarded endocrine secretions as a chemical extension of the nervous system. It is now becoming apparent that endocrinology, already closely connected with medicine and surgery, may link them with psychiatry as well.

There are certain periods during the life of an individual at which, for various reasons, additional strains are imposed on bodily health. Not infrequently, mental abnormalities may make their appearance during these periods of adjustment; sometimes they may occur alone, but more often in conjunction with physical disorders. In this respect both puberty and the menopause are of special interest to the psychiatrist.



### Medicine and Psychiatry.

The general advances made by medicine and surgery have resulted in a prolongation of the average life span. This has been acknowledged by the increased importance of geriatrics. Recent advances in medical therapeutics, particularly the use of antibiotics, have done much towards increasing life expectancy. Diseases of old age include degenerative conditions, not the least of which are mental disorders, such as cerebral degenerative changes and the sequelae of cardio-vascular disease. Psychiatry, therefore, has increased in stature as one result of these medical advances. In addition, the role of mental factors as a cause of vascular changes has already been described.

Modern psychiatry is taking more and more interest in disorders arising at the other end of life's span. By this means it is coming to take its place in paediatrics. The increasing importance of the origin of mental disorders in early childhood has intensified the interest of psychiatry in the earliest years of life. An instance just reported is that of the toxic effect of lead, in infancy, producing mental impairment later in school children.

A further group of diseases of special interest both to medicine and to psychiatry are those which are effective in the ante-natal period. The effect of rubella, during the first ten weeks of pregnancy, in producing congenital defects of the brain, heart and eye, is one of comparatively recent discovery. Congenital syphilis and meningitis or encephalitis during fetal life or infancy are not infrequently followed by characteristic disorders of intelligence and behaviour.

It is a consequence of this scientific age, which has arisen through the search for truth by reason and experiment, that facts discovered earliest would be those manifesting their presence by material change. This has initiated a sequence of events. Firstly, effects were noticed and the explanation of their causes was sought. When the effect had come from a material change, this was detected and associated more readily than in the cases in which no structural or material cause was acting. When numerous examples had been found in which cause and effect were obvious, it was assumed that all effects must show a structural alteration.

This has happened with both medicine and surgery. The search for causes of illness and abnormality has brought to light the obvious conditions in which a change of some sort can be associated clearly with the effect it produces. In this way congenital abnormalities, trauma, atrophy and degeneration, vascular alteration, bacterial and parasitic infection and neoplasms have been identified and associated with the conditions by which they are manifest.

But the careful study of these conditions, and of the symptoms they produce, has not fully explained all the illnesses and disorders that are encountered in practice. No matter how hard has been the attempt to account for each case by some physical change, it has become apparent that in some cases this cannot be done.

Medicine and surgery have now reached this stage and found several instances in which disorders may be present without material change. These are disorders due to functional change alone. It is to this group of disorders that psychiatry pays particular attention.

The stage that is now arising is the search for purely functional causes of illness and disorder, one of the most recent examples of which is given by Selye's conceptions of disorders arising from continued stress. Instead of waiting in the background to be used when other methods have been tried and found wanting, psychiatry is now taking the initiative and producing positive results.

Both in medicine and in surgery, preventive treatment is always to be preferred to the treatment of established disease. Social medicine, which includes the patterns of disease in a population in relation to the environmental culture and occupation, is particularly concerned with prevention. Psychiatric studies form a large section of those used, and problems such as the enforced loneliness and unhappiness of elderly retired persons, which may lead

to both mental and physical illness, are considered carefully in the hope and expectation of finding a satisfactory solution.

Alcoholism, one of social medicine's largest problems, leads to serious organic disorders. Psychiatric investigation is making it apparent that the underlying cause is an attempt by the individual to escape mental disturbances or worries. Psychiatric treatment, in the early stages, offers a more favourable outlook than medical treatment of chronic sufferers. Drug addiction is another disorder in which psychiatry and medicine, working in union, will aid one another.

Social medicine is concerned with human behaviour and its relationship with causes and consequences of disease. Schizophrenia, affective disorders and anxiety states are problems included in social medicine.

Surgical conditions connected with mental disturbance include suicide, while accidents, particularly those in industry, occur more frequently in individuals of a certain mental temperament, which acts as a predisposing cause. Psychiatric examination of accident-prone individuals is of value in identification of the tendency and enables preventive measures to be instituted.

In the search for preventive measures psychiatrists have examined various occupations and have shown that certain professions are more prone to particular diseases than others. For example, those entailing high responsibility or heavy mental strain and worry—such as that of business executives and members of the medical profession—are more liable to produce coronary disease and diseases of the alimentary tract. Individuals in these professions can consequently be more carefully watched and safeguarded when the earliest signs of these disorders become manifest.

The development of psychiatry has been from the position at which it was one of the most spurned and neglected of medical subjects to its present condition, in which it takes its place conjointly with the other branches of medicine. It has invaded many fields, often because of the inadequacy of prior competitors rather than through aggression. Its interests are widespread, for it seeks to understand mental problems arising from the whole environment in which man lives and which he makes for himself. Social, political, racial and international problems all have something to gain by reference to this subject.

To hold a steadfast course, psychiatry needs constantly to refer its subject matter back to the scientific foundations with which it is connected. Anatomy, physiology, neurology and experimental research form a sound basis for this. The purpose of this essay, which holds much controversial matter, is an attempt to show how this can be done.

### THE STABILITY OF COAGULATION FACTORS IN STORED BLOOD.

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THE physiology of blood coagulation has received much attention in recent years. Considerable advances have been made in that subject with the discovery of additional clotting factors, and of deficiency states produced by their absence. It is now widely recognized that the first stage in coagulation, the formation of plasma thromboplastin, is brought about by the combination of platelet factor with at least two plasma factors, in the presence of calcium (Biggs and Macfarlane, 1953a). The first of these plasma factors is antihæmophilic factor, and the second is Christmas factor, and deficiency of either of these factors is responsible for hæmophilia and for Christmas disease respectively. The second stage in coagulation is the conversion of prothrombin to thrombin under the influence of plasma thromboplastin and calcium. This stage also requires the presence of two plasma factors.



The first is factor V (labile factor) and the second is factor VII, a stable substance which is present in serum. Factor V has been studied extensively by Stefanini (1951), who demonstrated diminution of its activity in the blood in the post-operative period and in hepatic disease. Factor VII is also of great importance, since it is the factor selectively depressed by dicoumarol and its more recent derivatives.

The stability of these clotting factors on storage is a question of considerable importance, in view of the widespread use of stored blood for transfusion purposes. Direct transfusions have practically disappeared from clinical practice, blood used for transfusion having been collected previously and stored for varying periods of time before use. In New South Wales, blood collected into acid citrate dextrose medium is distributed by the Red Cross Blood Transfusion Service. Blood that is unused seven days after collection is withdrawn from use and is converted into serum. In other countries—for example, Great Britain—blood is stored for longer periods before it is withdrawn from use. During the period between collection of blood from donors and its administration to patients, a certain amount of deterioration occurs in the various clotting factors. This is well recognized by clinicians, who frequently order freshly collected blood for their patients. In hæmophilia the use of fresh blood has been regarded as highly important, in view of the lability of the anti-hæmophilic factor. In other instances, requests for fresh blood have been made on less acceptable grounds. It is the purpose of this study to ascertain whether any significant deterioration occurs in the various plasma factors when blood has been collected into acid citrate dextrose solution and stored in the method customary in blood transfusion services.

#### COLLECTION OF ACID CITRATE DEXTROSE BLOOD FOR TESTING.

Blood was collected aseptically from five donors into a bottle containing 37.5 millilitres of acid citrate dextrose solution. Each donor contributed about 45 millilitres, the total volume of the pooled blood together with anticoagulant being 250 millilitres. The acid citrate dextrose solution was the routine mixture used in the Red Cross Blood Transfusion Service, being composed of 3% disodium citrate and 3% dextrose in distilled water. The proportions of blood to anticoagulant were those in routine use.

Blood collected in this manner (ACD blood) was stored at 6° C. in a cold room. Estimations of factor V, anti-hæmophilic factor, prothrombin and factor VII were carried out at varying periods after collection. In order to estimate factor V, small samples of blood were removed on successive days and centrifuged to obtain the plasma, which was tested immediately for factor V activity. With regard to the other factors, it was found convenient to obtain samples of plasma in small bottles on the day of collection and on subsequent days, and to keep the plasma samples in a frozen state at -10° C. until the assays could be performed. The samples separated and frozen on the day of collection were used as controls in all the assays except those of factor V. In estimating factor V, freshly collected mixed samples of acid citrate dextrose blood were used as the controls.

#### COLLECTION OF OXALATED BLOOD FOR TESTING.

Assays of factor V were also carried out on oxalated blood. For this purpose blood from five donors was collected into 25 millilitres of 0.1M sodium oxalate solution, the total volume of blood with anticoagulant being 250 millilitres. The blood was stored at 6° C. and samples were removed for testing in the same manner as described for ACD blood.

#### CHANGES IN FACTOR V ON STORAGE.

##### Materials.

1. Stored oxalated plasma. Blood was collected from five donors into 0.1M sodium oxalate solution in a proportion of nine parts of blood to one part of oxalate solution. The plasma was separated by centrifugation and

was allowed to stand in open glass tubes for fifteen days at 4° C. It was then collected in small bottles and kept in the frozen state at -10° C. until required.

This plasma was used as a diluent free of factor V, storage of oxalated plasma at refrigerator temperature for fifteen days leading to virtual disappearance of this factor (Stefanini, 1951).

2. Fresh oxalated plasma. This was used for control purposes. The method of collection was as described previously. After separation by centrifugation, the plasma was used for testing within one hour of collection.

3. Fresh ACD plasma. This was used for control purposes. Blood was collected from five donors into ACD solution in a proportion of 8.5 parts of blood to 1.5 parts of ACD solution. After separation by centrifugation the plasma was used for testing within one hour of collection.

4. Thromboplastin. The thromboplastin used was prepared from rabbit brain by the Commonwealth Serum Laboratories.

5. Calcium chloride. Calcium chloride solution, 0.02M, was used.

#### Method of Estimation of Factor V.

Estimations of factor V were carried out daily on (i) oxalated and (ii) ACD blood collected and stored in the manner described.

The method used was that of Stefanini (1951). In that method, Quick one-stage prothrombin times are estimated on a mixture of one part of the test plasma in nine parts of stored oxalated plasma, the latter acting as a diluent free of factor V, but containing adequate amounts of the other clotting factors concerned in the reaction. The result was converted into a percentage by comparison with a graph obtained by estimating the factor V time of fresh plasma prepared in 100%, 50%, 25% and 12.5% strengths by dilution with physiological saline, each dilution then being again diluted 1 in 10 with stored oxalated plasma before performance of the test. Since the other clotting factors are supplied by the stored oxalated plasma, the various strengths of the control plasma may be regarded as identical, for practical purposes, with the concentration of factor V, and are interpreted accordingly.

When estimations were performed on oxalated plasma, fresh oxalated plasma was used for control purposes.

In all instances readings were taken in triplicate.

#### Results.

##### Oxalated Blood.

The results of two separate trials are shown in Table I. It is clearly shown that there is a rapid drop in factor V activity within the first two days, the level falling to 50% or lower. Thereafter the fall in activity is somewhat less rapid, but is still quite pronounced, the level at the end of one week being 10%. These experiments confirm the lability of factor V in oxalated plasma, which has been demonstrated by Stefanini (1951) and previous workers.

##### ACD Blood.

The results of two separate trials are shown in Table II. There is a great difference between the behaviour of factor V in ACD blood and that of the same factor in oxalated blood. Factor V is much more stable in ACD blood, very little deterioration occurring during the first three days. At the end of nine days the level of factor V is 45% to 50%. At the end of twenty-one days it is still 20% or over.

#### CHANGES IN ANTIHÆMOPHILIC FACTOR ON STORAGE.

##### Materials.

1. Hæmophilic plasma. Blood was collected aseptically from a hæmophilic patient into acid citrate dextrose medium. The plasma was separated by centrifugation and was collected into small bottles. It was then kept in the

frozen state at  $-10^{\circ}\text{C}$ , small quantities being thawed rapidly and used for testing as required.

2. Prothrombin-free plasma. This was used as a source of fibrinogen. Fresh oxalated plasma was rendered prothrombin-free by the addition of powdered barium sulphate in a proportion of 0.1 gramme of barium sulphate per millilitre of plasma, vigorous shaking for two minutes, incubation at  $37^{\circ}\text{C}$  for twenty minutes with occasional shaking and separation of the supernatant plasma by centrifugation.

TABLE I.  
Factor V Content of Oxalated Blood after Storage.<sup>1</sup>

Days After Collection.	Factor V—Time of Normal Plasma (Seconds).				Test Plasma.	
					Factor V Time. (Seconds.)	Per- centage.
	100%	50%	25%	10%		
Trial I.						
1	20	24	—	—	23	62.5
2	—	27	—	—	27	50.0
4	—	30	35	—	34	30.0
7	—	—	—	40	41	10.0
Trial II.						
2	—	24	29	—	26	40.0
3	—	23	27	—	27	25.0
7	—	—	—	37	37	10.0

<sup>1</sup> The prothrombin time of the stored oxalated plasma used as diluent was 65 seconds, which would correspond to a negligible content of factor V.

#### Methods.

Two methods were employed in the estimation of antihæmophilic factor. The first was a technique based on prothrombin consumption, and the second method employed the coagulation time of recalcified plasma.

TABLE II.  
Factor V Content of ACD Blood after Storage.

Days after Collection.	Factor V—Time of Normal Plasma (Seconds).				Test Plasma.	
	100%	50%	25%	12.5%	Factor V Time. (Seconds.)	Per- centage.
Trial I.						
1	28	—	—	—	27	Over 100
2	26	31	—	—	27	90.0
3	27	30	—	—	28	87.5
9	25	30	35	—	31	45.0
10	—	28	34	—	29	46.0
14	—	32	36	—	35	31.0
21	—	30	36	—	34	33.3
Trial II.						
2	24	29	—	—	25	90.0
3	24	28	—	—	25	87.5
7	23	30	—	—	28	64.0
9	—	32	—	—	32	50.0
10	—	32	—	—	32	50.0
15	—	30	38	—	34	37.5
21	—	—	38	55	45	20.0

#### First Method.

**Principle.**—The method is based on the fact that prothrombin consumption is negligible if hæmophilic plasma is allowed to clot, and that it is restored to normal if normal plasma has been previously added to the hæmophilic plasma. Prothrombin consumption becomes optimal in those circumstances, except when very high dilutions of normal plasma are used, in which case it is only partially corrected. When suboptimal amounts of normal plasma

are used, differences occur in the prothrombin consumption of hæmophilic plasma which can be correlated with the amounts of normal plasma that have been added, and therefore with the amount of antihæmophilic factor present in the mixture. For example, if the amount of antihæmophilic factor (AHF) in one five-hundredth part of control plasma is arbitrarily termed "100% AHF", then that contained in one one-thousandth part will be "50% AHF", and that contained in one two-thousandth part will be "25% AHF". A graph may then be constructed of the prothrombin times of the serum of hæmophilic plasma with the addition of one five-hundredth, one one-thousandth and one two-thousandth part of control plasma, each representing 100%, 50% and 25% AHF respectively. The prothrombin time of the serum of hæmophilic plasma after the addition of one five-hundredth part of the test plasma is then estimated, and the corresponding value on the graph is converted into terms of a percentage of AHF.

TABLE III.  
AHF Content of ACD Blood after Storage: First Method.

Days after Collection.	Prothrombin Time of Serum of Control Mixtures (Seconds).			Test Mixtures.		
	100% AHF.	50%	25%	Prothrombin Time of Serum. (Seconds.)	Percentage of AHF.	Average Percentage of AHF.
1	28	19	—	21.0	61.0	77.0
	25	19	—	23.5	87.5	
	27	18	—	24.0	83.3	
2	27	21	—	24.0	75.0	74.0
	23	15	—	21.0	87.5	
	27	16	—	18.0	60.0	
7	—	26	19	26.0	50.0	55.0
	—	22	16	24.0	58.0	
	24	17	—	18.0	56.0	
16	—	22	19	19.0	25.0	27.5
	—	45	25	29.0	30.0	

**Technique.**—Six glass tubes, each containing one millilitre of freshly thawed hæmophilic plasma, were placed in a water bath at  $37^{\circ}\text{C}$ . To each of two pairs was added 0.1 millilitre of diluted normal plasma, these being the control tubes; 0.1 millilitre of diluted test plasma was added to each of the third pair of tubes. Each tube was recalcified by the addition of 0.1 millilitre of 4.4% calcium chloride solution. After clotting had occurred, the tubes were incubated at  $37^{\circ}\text{C}$  for a further fifty minutes. The clots were then gently separated from the walls of the tubes, which were centrifuged at high speed for three minutes. The serum in each pair of tubes was then separated from the clot, pooled, and allowed to stand in a glass tube until the completion of an hour after clotting. Prothrombin estimations were then performed in triplicate on each sample of serum. Prothrombin-free plasma was used as the source of fibrinogen.

**Results.**—The results are shown in Table III. The concentration of antihæmophilic factor is shown to drop steadily during storage. During the first two days the loss of antihæmophilic factor is not very pronounced. By the seventh day, however, the level is approaching 50%, and by the sixteenth day it is in the region of 25%. These results must be compared with those obtained by the second method.

#### Second Method.

**Principle.**—In hæmophilia the calcium time (that is, the coagulation time of recalcified plasma) is greatly prolonged compared with that of normal subjects. However, the addition of small quantities of normal plasma prior to recalcification produces appreciable shortening of the calcium time, and the content of antihæmophilic factor of a sample of stored plasma may be estimated by comparison of its corrective action on the calcium time of hæmophilic plasma with that of appropriate dilutions of control plasma when similarly added to hæmophilic plasma.

**Technique.**—The reagents were as follows: (i) hæmophilic ACD plasma; (ii) normal diluted ACD plasma (control and test); (iii) 0.02M calcium chloride solution. A mixture of 0.1 millilitre of hæmophilic plasma and 0.1 millilitre of diluted normal plasma was recalcified by the addition of 0.2 millilitre of 0.02M calcium chloride solution and the clotting time at 37° C. was estimated. The dilution of normal plasma used as a standard—that is, taken to represent 100% AHF—differed in different estimations.

TABLE IV.  
AHF Content of Stored Blood: Second Method: Trial I.<sup>1</sup>

Days after Collection.	Calcium Times of Control Mixtures (Seconds).		Test Mixture.	
	100% AHF.	50% AHF.	Calcium Time (Seconds.)	Percentage of AHF.
Scale: 10% Dilution of Control Plasma, 100% AHF; 5% Dilution of Control Plasma, 50% AHF; Test plasma used in 10% dilution.				
1	114	135	120.0	86.0
2	114	135	131.0	60.0
5	114	135	128.5	65.0

Scale: 5% Dilution of Control Plasma, 100% AHF;  
2.5% Dilution of Control Plasma, 50% AHF;  
Test plasma used in 5% dilution.

1	135	147	133.0	Over 100
2	135	147	144.0	62.5
5	135	147	145.5	56.0

Scale: 2.5% Dilution of Control Plasma, 100% AHF;  
1.25% Dilution of Control Plasma, 50% AHF;  
Test plasma used in 2.5% dilution.

1	147	185	149.0	97.0
2	147	185	176.0	61.0
5	147	185	168.0	72.0

Average.

Days after Collection.	Percentage of AHF.
1	94.0
2	61.0
5	64.0

<sup>1</sup> Results were obtained in triplicate and averaged. For day 5, the average of six determinations is shown.

However, in most of them it was found satisfactory to use 0.1 millilitre of a 10% dilution of the control plasma in physiological saline as representing 100% AHF, and the same volume of a 5% dilution as representing 50% AHF. The hæmophilic plasma and normal plasma reagents (test and control) were used as soon as possible after being thawed and were kept in an ice bath throughout the tests. A fresh bottle of hæmophilic plasma was thawed and used for each series of determinations.

**Results.**—The results of two separate series of determinations are shown in Tables IV and V. The findings are comparable with those obtained by the previous method. There is very little deterioration after one day's storage, but after two days the level has fallen considerably. At the end of eight days it is in the region of 50%, and after twelve days it is still lower. Certain discrepancies are present. It is noted, in both determinations, that the level of AHF is apparently higher after five days than after two days. A much more striking finding is the very high result obtained on plasma after sixteen days' storage. This finding was not present when the method of prothrombin consumption was used, but

was confirmed on different samples of plasma on several occasions by the method in which calcium times are employed. The explanation is probably technical, and the phenomenon may be due to formation of accelerators in the plasma being tested.

Summary of Results.

The results of the various determinations are shown in Table VI.

TABLE V.  
AHF Content of Stored Blood: Second Method: Trial II.<sup>1</sup>

Days after Collection.	Calcium Times of Control Mixtures (Seconds.)			Test Mixtures.	
	100% AHF.	50%.	25%.	Calcium Time (Seconds.)	Percentage of AHF.
1	139	162	174	137.0	Over 100
2	139	162	174	157.0	61.0
5	139	162	174	154.5	66.0
8	139	162	174	162.0	50.0
12	139	162	174	166.0	42.0
16	139	162	174	149.0	78.0 <sup>2</sup>

<sup>1</sup> Averages of three determinations shown. For day 5, average of six determinations shown. Scale: 10% dilution of control plasma, 100% AHF; 5% dilution of control plasma, 50% AHF; 2.5% dilution of control plasma, 25% AHF; test plasma used in 10 dilution.

<sup>2</sup> Technical factors probably responsible.

When allowance is made for the differences between the two methods, and for the technical difficulties and inaccuracies, which are considerable, the position may be stated as follows.

Deterioration of antihæmophilic factor in the first day of storage is only slight. Thereafter it becomes appreciable and at the end of a week the level is approximately 50%. After the end of a week further deterioration takes place, and at the end of sixteen days the level is probably in the region of 25%.

TABLE VI.  
AHF Content of Stored Blood: Summary of Results.

Method.	Day.	AHF Content.
First method: Prothrombin consumption technique.	1	77.0%
	2	74.0%
	7	55.0%
	16	27.5%
Second method: Calcium time technique:		
	Trial I .. .. .	
	1	94.0%
	2	61.0%
	5	64.0%
	Trial II .. .. .	
	1	Over 100%
	2	61.0%
	5	66.0%
	8	50.0%
	12	42.0%
	16	78.0% <sup>1</sup>

<sup>1</sup> See earlier section.

The significance of these findings in relation to the efficacy of stored blood in hæmophilia will be discussed further in a later section.

CHANGES IN PROTHROMBIN ON STORAGE.

Materials.

1. Prothrombin-free oxalated plasma. This was prepared from fresh oxalated plasma by means of barium sulphate, as described in a previous section. In an effort to ensure that it was completely prothrombin-free, the procedure was carried out twice. This reagent failed to clot after the addition of thromboplastin and calcium.

2. Serum. This had been prepared from blood by the addition of calcium chloride. It had been standing at



room temperature for one month. The serum was diluted by the addition of four parts of physiological saline before use.

3. *Thromboplastin*.—Thromboplastin derived from rabbit brain was used. With this thromboplastin the prothrombin time of fresh oxalated plasma was 17 seconds.

4. Calcium chloride solution, 0.02M.

#### Method.

The principle is to obtain a mixture containing all the coagulation factors except prothrombin, which therefore has a greatly delayed prothrombin time. If prothrombin is supplied by adding diluted normal plasma to the mixture, the prothrombin time is shortened. This method compares the shortening of the prothrombin time of a prothrombin-poor mixture by adding a given dilution of control plasma with that obtained by adding the same dilution of test plasma.

The prothrombin-poor mixture consisted of 0.1 millilitre of barium sulphate plasma and 0.1 millilitre of serum diluted one in five. The former reagent supplied fibrinogen and factor V, the diluted serum supplying factor VII. To this mixture was added 0.1 millilitre of control or test plasma at the appropriate dilution, and the prothrombin time was then obtained by adding 0.1 millilitre of thromboplastin and 0.1 millilitre of 0.02M calcium chloride solution at 37° C. An amount of 0.1 millilitre of 10% control plasma was taken as representing 100% prothrombin, and the same volume of 5% control plasma represented 50% prothrombin. The test plasma was added in a dilution of 10%.

#### Results.

The prothrombin-poor mixture gave a greatly delayed prothrombin time of sixty seconds. Traces of prothrombin remaining in the serum were probably responsible for the fact that clotting occurred.

Considerable shortening of the prothrombin time was produced by adding the diluted control or test plasma. Results of the prothrombin assays on the test plasma are shown in Table VII. It is shown that prothrombin is stable, deteriorating on storage only at a slow rate. At the end of sixteen days the level is approximately 67%.

TABLE VII.  
Prothrombin Content of Stored Blood.

Days after Collection.	Prothrombin Time of Control Mixture (Seconds).		Test Mixture.	
	100% Prothrombin.	50% Prothrombin.	Prothrombin Time (Seconds.)	Prothrombin Percentage.
1	30	36	31	92.0
8	30	36	32	83.0
12	30	36	32	83.0
16	30	36	34	67.0

#### CHANGES IN FACTOR VII ON STORAGE.

##### Material.

1. Seitz-filtered ACD plasma. Fresh ACD plasma was Seitz-filtered, collected in small bottles, and stored in the frozen state at -10° C. until required. This reagent supplied fibrinogen and factor V, and also prothrombin in fairly small quantities, but contained no factor VII. This reagent failed to clot after thromboplastin and calcium had been added.

2. Thromboplastin and 0.02M calcium chloride solution, as before.

##### Method.

The prothrombin time of the Seitz-filtered plasma was estimated after it had been shortened by the addition of diluted control and test plasma in quantities of 0.1 millilitre. This volume of 10% control plasma was taken as supplying 100% factor VII, the same volume of 5% control

plasma supplying 50% of factor VII. The test plasma was added in a dilution of 10%.

#### Results.

The results are shown in Table VIII. Factor VII is very stable on storage, only slight deterioration being demonstrated at the end of twelve days.

#### ALTERNATIVE METHODS OF ASSAYING ANTIHÆMOLYTIC FACTOR.

Considerable technical difficulties have been experienced in this type of assay, and various alternative methods were tried and abandoned before satisfactory results were obtained. Methods investigated were the thromboplastin generation test (Biggs and Douglas), the thrombin generation test (Pitney and Dacie), a modified calcium time method (Soulier and Larrieu), and the partial thromboplastin time (Brinkhous *et alii*).

TABLE VIII.

Days after collection.	Prothrombin Time of Control Mixture (Seconds.)		Test Mixture.	
	100% Factor VII.	50% Factor VII.	Prothrombin Time (Seconds.)	Percentage of Factor VII.
1	38	54	39	97.0
2	38	54	39	97.0
5	38	54	41	91.0
8	38	54	42	87.5
12	38	54	43	84.5
16	38	54	38	100.0 <sup>1</sup>

<sup>1</sup> This plasma sample had been previously thawed and refrozen. This result is probably due to the activation of accelerators from their less active precursors.

The thromboplastin generation test was performed as described by Biggs and Douglas, with the exception that barium sulphate was used instead of aluminium hydroxide to prepare prothrombin-free plasma. It was found necessary to dilute the samples of prothrombin-free plasma (control) with physiological saline to a strength of 1 in 50, 1 in 100, and 1 in 200 in order to obtain a satisfactory standardization curve. The method in our hands gave inaccurate results and was discarded.

The thrombin generation test was found to be too tedious and insufficiently quantitative and was abandoned for those reasons. The more recent modification of that test, in which pyrocatechol reagent is used to inhibit serum anti-thrombin (Fantl and Sawers, 1954), was not available when these studies were performed.

The calcium time method of Soulier and Larrieu was found to give consistent results. The calcium time method eventually adopted was identical with the method of Soulier and Larrieu, except for the omission of the platelet factor reagent. In these studies the hæmophilic plasma reagent was not platelet-free, and a separate platelet reagent was not necessary. Since the hæmophilic plasma was all collected on the one occasion from the same donor, and was stored frozen in small bottles, the amount of platelet factor present in different estimations was constant.

The partial thromboplastin method of Brinkhous *et alii* was next investigated. These authors have described the effect of "partial" thromboplastins, such as cephalin and Russell viper venom, which, in contrast to "complete" thromboplastins such as human and rabbit brain, clot hæmophilic plasma slowly, although their action on normal plasma is powerful. This effect is present to a limited extent with "complete" thromboplastins at high dilutions. With "partial" thromboplastins, however, it is much more pronounced and is observed at low dilutions as well. Brinkhous and his associates have devised a method for estimating antihæmophilic factor by comparing the corrective effect of control and test plasma on the prolonged "partial" thromboplastin time of hæmophilic plasma.



"Stypven" was tested at low and high dilutions on hæmophilic and normal plasma for its suitability as a "partial" thromboplastin. However, it was found to act as a "complete" thromboplastin when diluted 1 in 1000. At this strength the "partial" thromboplastin time was only slightly longer for hæmophilic plasma than for normal plasma—an effect no greater than that obtained with human or rabbit brain at the same dilution. No other "partial" thromboplastins were available and the method was not used.

#### DISCUSSION.

The stability of proteins is a chemical problem of considerable practical importance. The behaviour of coagulation factors in stored blood is only one aspect of this problem.

The plasma proteins may be subdivided into albumins and globulins. Albumins are chemically stable, whereas globulins are less stable and are subject to denaturation on storage. All naturally occurring coagulation factors are globulins.

The decomposition of plasma proteins on storage can be delayed in various ways. The most effective method is lyophilization. Unstable proteins such as thrombin may be preserved for several years after being freeze-dried and are found to be physiologically active when redissolved in water. Proteins in solution deteriorate more rapidly. Freezing delays the process considerably, but does not prevent it. However, unstable globulins may be preserved for several months in the frozen state.

The various globulins associated with blood coagulation vary considerably in stability. Fibrinogen is fairly stable and does not deteriorate when kept for short periods, as is done in the case of blood used for transfusion. The deterioration of fibrinogen is gradual, occurring over some weeks or months, and is accompanied by the formation of a fibrous or gelatinous deposit resembling fibrin. The nature of this material has been the subject of some discussion. It is probable that the denaturing of fibrinogen takes the form of slow polymerization, with the eventual formation of fibrin together with various intermediate products. Fibrinogen itself may be precipitated at low temperatures when in high concentration. This process is greatly assisted by the presence of alcohol or ether, and is the basis of the preparation of fibrinogen fraction during plasma fractionation. The precipitation of fibrinogen under these circumstances is, of course, reversible, being merely a physical change unaccompanied by denaturation of the molecule.

Prothrombin is a moderately stable substance, which does not deteriorate appreciably in the first fortnight of storage. Factor V, on the other hand, is labile, and it has been shown to deteriorate very rapidly in oxalated blood. However, in acid citrate dextrose medium it is much more effectively preserved, and the level does not fall below 50% until after the ninth day of storage—that is, well after the period when blood intended for transfusions has been time-expired and withdrawn from use. The clotting factors whose activity is measured by the Quick one-stage prothrombin technique (factor V, prothrombin and factor VII) are present in considerable excess in plasma. It is well known that the prothrombin time of whole plasma is lengthened only by a second or so by dilution of the plasma with an equal quantity of saline; this indicates that a fall to 50% in the concentration of each of the three clotting factors taking part in the reaction does not cause more than a trifling disturbance in the coagulation mechanism. One may conclude with the opinion that factor V is supplied in adequate amounts in transfused blood stored for up to seven days, and that there is no need to obtain fresh blood for the sake of this factor except in cases of congenital factor V deficiency.

With regard to factor VII, it is well known that this factor is extremely stable. Aged serum is a good source of supply for factor VII and is used as a laboratory reagent for this purpose. In the present investigations only slight deterioration was demonstrated in ACD blood

in a fortnight of storage. It was mentioned earlier that factor VII is the factor that is selectively depressed by dicoumarol and allied drugs. One still sees the recommendation that in hæmorrhagic states produced by over-dosage of dicoumarol, the patient should be transfused with fresh blood. Stored blood and aged serum are just as good a source of factor VII as fresh blood, and should be just as effective in these cases. One's own preference would be to use blood rather than serum, since there is also some depression of prothrombin by the end of a week of dicoumarol therapy, but not to insist that it be freshly collected.

The stability of Christmas factor in ACD blood was not investigated in this study. It is well known that this factor is stable, being present in high concentration in aged serum. This substance is closely related chemically to factor VII, and its stability on storage probably follows the same pattern.

The most important coagulation factor with regard to hæmorrhagic disorders is antihæmophilic factor. The nature of the hæmorrhagic state in this disorder is less simple than used to be imagined. It is paradoxical that *in vitro* normal clotting can be restored to hæmophilic blood by the addition of a mere fraction of normal blood or plasma, whereas on the other hand, severe hæmorrhages in hæmophilic patients may persist in spite of the transfusion of many pints of blood.

This phenomenon has not been satisfactorily explained. One suggestion has been that insufficient antihæmophilic factor is present in the transfused blood. This does not account for the lack of success at times when many pints of fresh blood have been given.

Another suggestion has been that the citrate in transfused blood when given in large amounts interferes with the coagulation mechanism of the recipient. There is no scientific justification for this view, for the following reasons. The citrate ion acts as an anticoagulant *in vitro*, through its combination with calcium ions to form a non-ionized compound. The removal of calcium ions from the blood of a living subject produces tetany long before any disturbance of coagulation becomes apparent. Tetany does not occur in persons receiving blood transfusions. Furthermore, the body is capable of the rapid metabolism and destruction of citrate. Citric acid is important in the metabolism of carbohydrate, being one stage in the Krebs cycle; and there are efficient mechanisms for its breakdown.

A third suggestion is that inhibitors of coagulation occur in hæmophilia and are responsible for refractoriness to transfusions. It has been demonstrated that, in a number of cases, circulating anticoagulants have developed in patients with hæmophilia, these being antibodies produced in response to antihæmophilic factor supplied in transfused blood. In the vast majority of hæmophiliacs, however, no anticoagulants can be demonstrated.

In summary, no satisfactory explanation has yet been offered for the refractoriness of some cases of hæmophilia. It is probably associated with total lack of antihæmophilic factor in these patients, but there must be some other explanation as well.

With regard to the content of antihæmophilic factor in transfused blood, the present investigations have shown that, although deterioration does occur to a significant degree, considerable activity is still present at the end of a week. There is no significant fall in this factor until the second day after collection. At the end of a week the level of antihæmophilic factor is about 50%. These findings agree fairly closely with the results obtained by Pitney and Dacie (1953). These workers, using the method of thrombin generation, found that there was no appreciable fall in antihæmophilic factor after twenty-four hours, and that the level reached 50% by the twelfth day.

These investigations suggest that if it was merely a question of replacing a missing factor it should be easy to check hæmorrhage in hæmophilia by the use of blood collected and stored in the routine way. That such is not the case has been demonstrated clinically on numerous occasions. It is essential, in dealing with hæmorrhagic

states in hæmophilia, to supply blood with as high a content of antihæmophilic factor as possible. This can be done by transfusing patients with blood collected within the previous twenty-four hours.

Effective hæmostasis requires the presence of adequate numbers of platelets, in addition to the plasma coagulation factors. Platelets are very poorly preserved in blood collected in the usual manner, since they disintegrate rapidly on glass surfaces. Furthermore, citrate is not a good medium for the preservation of platelets. In blood collected in the routine way platelets survive in fairly large numbers for some hours. However, their viability is greatly impaired, and it is well known that transfusion of blood and of packed red cells does not cause any rise in the platelet count in thrombocytopenic recipients. Attempts have been made in the last two years to transfuse viable platelets in these conditions. Polycythæmic or normal plasma collected in silicone-lined apparatus and plasma obtained by the use of "Sequestrene" as an anticoagulant have served as the source of platelets.

Platelet transfusions are very limited in their indications and effectiveness. Stefanini has demonstrated that platelets have specific groups, analogous to the blood groups. This work suggests that intergroup reactions are possible, with destruction of incompatible transfused platelets. Furthermore, Harrington and his associates have found that in idiopathic thrombocytopenic purpura there exists a mechanism in the patient's blood for the rapid destruction of normal platelets.

Disintegration of platelets does not lead to any loss of coagulability *in vitro*. On the contrary, blood in which platelets have broken down is more coagulable than formerly. In the present study, plasma used as a reagent for testing was preserved by freezing and then was thawed as required. This procedure causes total destruction of platelets, and it was found that the calcium time of the freshly thawed plasma was much shorter than that of the plasma when originally collected. Destruction of platelets causes liberation of platelet factor, together with platelet accelerators and a small amount of thromboplastin. Platelet factor is chemically stable, and probably remains active for many days. It is most unlikely that blood used for transfusions would develop any significant deficiency in platelet factor.

The main function of the platelet in hæmostasis is not, however, associated with the coagulation factors which it contains. Its principal importance is mechanical, since it acts as a plug in repairing breaches in capillaries. It also contains a vasoconstrictor material which acts in arresting circulation to injured areas. The mechanical function of platelets is lost when they disintegrate.

The importance of this aspect of platelet physiology is illustrated in the recent experiences of Aird and his associates (1954). These authors, together with others, have observed considerable bleeding towards the end of cardiac operations in which artificial heart-lung machines were used. They attributed the bleeding to a combination of a severe drop in the platelet count, which was noteworthy in their case, and in "dilution" of the patient's blood by transfusion with the stored "bank" blood which contains no platelets and may be deficient in factor V and in antihæmophilic factor. One disagrees with the "diluted" hypothesis except in so far as it affects platelets. The fact that bleeding is severe in spite of the abundance of platelet factor produced by the platelets destroyed in the heart-lung machine indicates the importance of intact platelets in hæmostasis, and it appears that this type of operation is one of the few real indications for platelet transfusion.

#### CONCLUSIONS AND SUMMARY.

The stability of coagulation factors in stored blood has been investigated. Factor V and antihæmophilic factor are relatively labile, whereas prothrombin and factor VII are stable. During the period when ACD blood supplied by the Red Cross Blood Transfusion Service is available for use—that is, up to one week after collection—the level of

factor V falls to about 60%, and that of antihæmophilic factor falls to about 50%. No significant fall occurs in antihæmophilic factor until the second day after collection. Prothrombin and factor VII do not deteriorate significantly for at least a fortnight.

The significance of these findings in relation to clinical problems has been discussed, with particular reference to hæmophilia.

#### ACKNOWLEDGEMENTS.

I am greatly indebted to the New South Wales Red Cross Blood Transfusion Service for providing the facilities for this study, and to Dr. R. J. Walsh for his helpful advice. I also wish to thank Dr. J. R. Reed, of the Royal Prince Alfred Hospital, for supplying hæmophilic blood from a patient under his care.

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#### PREMATURITY, THE OBSTETRICIAN'S RESPONSIBILITY.<sup>1</sup>

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THE advances of the first half of this century in general medicine and obstetrics have resulted in a great saving of infant life. In the obstetric hospitals we are now faced with the problem of trying to reduce even further our infant mortality. A limited improvement can be hoped for in the case of the mature baby, but there does remain one vast field—that of the premature baby. Approximately 60% of fetal mortality is associated with prematurity, and it is the greatest cause of fetal loss.

An International Committee at Geneva in 1937 stated that "Any infant weighing 5½ lbs or less at birth is regarded as a premature baby, regardless of the period of gestation". This will, of course, include a few small mature babies.

In order to reduce our loss of premature babies, we must (i) give better pædiatric care to them, (ii) conduct

<sup>1</sup>Read at a meeting of the New South Wales Branch of the Royal College of Obstetricians and Gynecologists with the Northern Districts Medical Association, Newcastle, February 28, 1953. Submitted for publication on May 6, 1955.

more skilled deliveries, (iii) better control the conditions that precipitate or necessitate premature labour.

In this study I have examined the records of all those premature babies born alive at the Women's Hospital, Crown Street, Sydney, in the year 1951-1952. There were 394 of them—an incidence of 7.1% of a total of 5552 live births. This is comparable with other centres, as will be seen from the following figures: Liverpool Maternity Hospital (1950), 7.6%; North Middlesex Hospital (1949), 7.5%; Rotunda Hospital, Dublin (1952), 8.8%; Queen Charlotte's Hospital, London (1951), 7.3%; Glasgow Maternity Hospital (1951), 11.1%.

In our series 10.6% of those premature babies died in the neonatal period; our mortality rate among mature infants was 0.4%. Other hospitals give the following neonatal mortality rates: Liverpool Maternity Hospital, 10.9%; North Middlesex Hospital, 26.3%; Rotunda Hospital, Dublin, 14.25%; Queen Charlotte's Hospital, London, 15.2%; Glasgow Maternity Hospital, 21.7%.

Drillien in Edinburgh (1947) showed that 25% of those premature infants that die, do so in less than six hours, and 50% in the first twenty-four hours. It is generally found that the routine care of the premature baby is unable to influence to any great degree the death rate in the first forty-eight hours.

The death rate is dependent on the following five factors: (i) the maturity of the baby, (ii) the weight of the baby, (iii) the presence and severity of maternal complications, (iv) birth trauma, (v) the presence of foetal abnormalities (a small group).

A study of our cases has been made, with the hope that some measures might be taken to prevent premature labour. We must attempt to give more mature babies into the care of our paediatricians.

The incidence of causative factors is set out in Table I.

TABLE I.  
Incidence of Causative Factors.

Causative Factor.	The Women's Hospital, Sydney, 1951-1952.	Mary Cross (Birmingham).
Spontaneous labour (no known cause) ..	28%	37%
Preeclamptic toxæmia .. .. .	23%	29%
Hypertensive toxæmia .. .. .	10%	9%
Multiple pregnancy .. .. .	9%	—
Placenta prævia .. .. .	8%	—
Accidental ante-partum hæmorrhage ..	5%	—

Other rarer, but definite, causes are the following: external version under anaesthesia, abnormal foetus, hydramnios, diabetes, anæmia, malnutrition, double uterus, hyperpyrexia.

The largest group is that of spontaneous labour. We know nothing about these cases as yet and can do little to prevent them. If the patient habitually comes into early labour she may be put to bed early and given oestrogens and progesterone. This will by no means always stop the onset of early labour.

The next largest group comprises the toxæmias of pregnancy. Work done at the Women's Hospital, Sydney, and published in its different aspects by T. Dixon Hughes, R. B. C. Stevenson and R. H. J. Hamlin, has shown that ante-natal care of the highest standard is almost eliminating eclampsia and greatly reducing the degree of preeclampsia. If this is accomplished there will be fewer small premature babies delivered after induced labour. Labour may have to be induced for preeclampsia, but we are able to induce it later in the pregnancy, and the babies are larger and less ill.

Figure I shows how the fall in premature infant mortality has fallen concomitantly with the fall in the eclampsia rate; of course, other factors are involved, but the great reduction in the number of sick premature babies

from mothers with severe preeclampsia and eclampsia is decisive.

Twins formed 9% of our series. However, we find that twins survive better than single babies of comparable weight; they are generally more mature. We analysed the mortality figures for 57 consecutive babies weighing three to four pounds born from single births, and compared them with those of 57 consecutive twin babies of the same weight group. The results were as follows: single baby mortality rate, 32%; twin mortality rate, 17.5%.

Professor T. N. A. Jeffcoate, in Liverpool, is admitting his patients with twin pregnancies to hospital at about the thirty-second week, hoping to prevent them from coming into labour. Many, of course, come into labour even if they are in bed.

In 1950-1951 we had 66 cases of twin pregnancy; 52% of these twins went to thirty-eight to forty weeks' gestation. In 1951-1952 we had 52 cases, and 54% went to thirty-eight to forty weeks. The mortality rate in the thirty-eight to forty weeks group was 1.6%. In the thirty to thirty-four weeks group (which was 13.5% of the whole) the mortality rate was 57%. However, we must remember

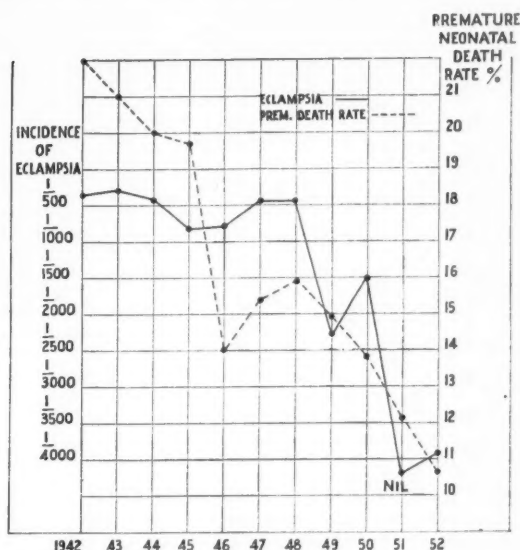


FIGURE I.

Incidence of eclampsia in "booked" patients, compared with the premature neonatal death rate, the Women's Hospital, Sydney.

that the maternal complication causing early labour, in twins as well as in single births, is frequently also a strong factor in the infant's death.

Professor C. H. G. Macafee's work in Belfast on the conservative management of *placenta prævia*, published in 1945, is monumental. By lack of interference, by recognition of the fact that the first hæmorrhage almost always stops before killing the baby or mother, by transfusion, by doing away with heroic manipulations to deliver the child, and by using Caesarean section or artificial rupture of the membranes near term, before labour starts a disastrous hæmorrhage, he has opened the way to the saving of many babies who would have been hitherto delivered hopelessly immature, and possibly in a state of shock.

Of our cases of prematurity, 8% were due to *placenta prævia*. Of these babies, 30% were delivered by Caesarean section, and all lived. Five babies were delivered by podalic version and breech extraction, and all died; but this method was used because of uncontrolled bleeding when the infants were very premature. Unfortunately the



presence of *placenta prævia* seems to precipitate spontaneous early labour. It is sometimes possible to stop labour with heavy sedation. Blood transfusions may be necessary to replace blood, and oxygen may be given to the mother for the baby's sake.

If the membranes rupture without labour before the thirty-sixth week, the mother should be put to bed and sedated, and given prophylactic chemotherapy. In a small number of cases pregnancy will continue for several weeks and the child become reasonably mature.

Professor D. Baird, of Aberdeen, has been writing for many years on the importance of malnutrition and a low living standard as a cause of prematurity. That probably is so in some countries, but I do not think we see much of it here. In our series only one case could be classified as due to malnutrition.

Before we consider the problems of premature labour and delivery it is interesting to note the post-mortem findings in 44 premature babies that died in the neonatal period. They are as follows: atelectasis, with or without a hyaline membrane, 23; cerebral hæmorrhage (intraventricular), 11; kernicterus (three cases of erythroblastosis), 4; congenital abnormalities, 4; pulmonary hæmorrhage, 2. Atelectatic areas are common in premature babies' lungs. They are usually due to blockage of a bronchus, to the thoracic musculature's being too weak, to some damage to the respiratory centre through cerebral œdema or hæmorrhage, or to sedation.

#### The Conduct of Premature Labour.

Ideally, the labour should be one of moderate duration and intensity; sedation and general anaesthesia are kept to a minimum. The poorly developed respiratory centre may be greatly depressed by anaesthesia.

It is well to explain the situation to the mother and try to persuade her to go through labour with minimal sedation. "Trilene", with a Friedman inhaler, and potassium bromide with chloral hydrate can be used, and the delivery conducted with pudendal local block. An episiotomy is usually performed in the case of *primiparæ* to prevent pressure on the soft head.

If labour is not progressing even after episiotomy, a very careful forceps delivery can be carried out under local infiltration anaesthesia.

At the Women's Hospital, if there is not time to inject the local anaesthetic, a few drops of chloroform are used for the delivery of the head. This procedure does not seem to harm the baby, but a full ether anaesthetic does. The mother should receive oxygen intranasally during delivery.

Some Americans hold that low spinal or caudal block should be used, as it not only gives an anesthetized and relaxed area for the delivery, but also reduces the power of the contractions; they lay great stress on this, and Masters and Ross report a 10.7% uncorrected fetal mortality rate in their spinal-caudal block series compared with 20.8% in the normally delivered series. However, Greenhill, of Chicago, considers that the maternal dangers of spinal and caudal block outweigh the advantages, and most of the staff at the Women's Hospital hold this view. Some caudal blocks have been used; but they absorb the obstetrician's time, there is considerable delay in labour, and many patients come to rotation and forceps delivery. We have not used spinal saddle block.

A further great cause of premature fetal death is cerebral hæmorrhage, usually intraventricular. Great care must be taken with the delivery of small babies. They are never to be considered "easy". The most skilled obstetrician available should conduct the labour and delivery. Spontaneous vertex delivery with episiotomy gives the best results.

The worst results come from version and breech extractions. The second of twins may suffer in this way. If the position has to be corrected by internal version, delivery should be allowed to come spontaneously.

Breech delivery of the premature infant holds its own special dangers: the imprisonment of the relatively large

head in the incompletely dilated cervix, and the precipitate delivery of the head over the perineum. The premature fetal body and shoulder girdle frequently has a smaller diameter than the head, and the body will slip through the cervix until obstruction comes round the baby's neck, with a tight cervix insufficiently dilated to allow the head through. This is a very serious complication, and many babies have been lost this way, either from asphyxia before delivery could be effected or from cerebral hæmorrhage due to the force needed to pull the head through. Amyl nitrite may dilate the cervix a little, but incision of the cervix at the 4 o'clock and 8 o'clock positions may have to be carried out if it is thin enough.

Special mention should be made here of Cæsarean section. Local infiltration or spinal anaesthesia is the best anaesthetic. The baby should be delivered by the vertex through an adequate incision; the head must not be avulsed suddenly through a tight incision by pulling on the feet. Preparations should have been made to receive the baby into warm clothes, and to suck the mucus from the airways. This is of great importance, as these babies do not cry properly and have little or no cough reflex, and can die of quite small mucous blockage. Intranasal oxygen apparatus or an oxygen tent should be available.

The baby should get all the cord blood possible. We measured the blood in a large number of cords cut early, and found it possible to "milk" 30 to 100 cubic centimetres from them. A premature baby will probably have a total blood volume considerably less than 300 cubic centimetres, and may be left quite anæmic if the cord is cut when full of blood.

#### Care of the Premature Baby.

Resuscitation of the baby is carried out in the operating theatre or in the anaesthetic room; there may be a great deal of fluid in the stomach and airways, and this should be aspirated with a small catheter. A cot fitted with oxygen cylinders is used so that the baby can have oxygen on the way from the theatre to the premature nursery.

In countries where domiciliary midwifery is the practice, as in parts of England, premature infant centres have been set up with special transport to pick the baby up and bring it to the centre under the best conditions. We have many premature babies sent to us at the Women's Hospital; most of them arrive in good condition, but not all. It is most important for us to realize that premature babies travel badly. It is not possible to give them adequate attention *en route*. Their oxygen supply may be intermittent, they become cold; they are bumped about, but most of all they become cold. We have seen a number of babies delivered to us so cold that it has taken many hours to warm them to normal temperatures, and some have not recovered their warmth or their lives. Babies are best transported *in utero*. If possible, send the mother for delivery into the hospital where the baby will be nursed, or consider carefully whether the baby may not be better nursed where it is born. If you intend to move the baby after birth, do so early rather than waiting for some days.

The care of premature babies requires specially trained and highly skilled nurses, but the most important requirement is a twenty-four hours' vigilance. The baby must never be nursed in a corner of a general ward where a sister looks at him in the course of her other duties. He must be in a good light night and day, and have someone near at hand at all times to watch for those sudden attacks of cyanosis which usually mean mucous obstruction of the larynx—so simple to remove, so fatal if it is not noticed at once.

#### Conclusion.

The premature nursery is usually a show place in a modern hospital—oxygen pipelines, incubators bought at great cost, resuscitators, oxygen tents, thermostats, humidifiers, ultra-violet light lamps, specially trained staff—all this impresses the lay visitor, but it is tragic that so many cots are needed here. In spite of all our skill and apparatus, many of these babies will die. It is

the object of this paper that obstetricians everywhere will be moved to find ways whereby the incidence of prematurity is reduced, and babies are delivered safely and near term and ready for extrauterine life.

#### Acknowledgements.

I wish to thank Dr. T. Dixon Hughes and Dr. John Chesterman, who read this paper and made valuable suggestions; also Dr. S. E. L. Stening, under whose skilled care these babies come; and Sister B. Gibbes and her premature nursery staff, whose experience has taught me much about these babies, and whose special interest in this problem has made the low death rate among premature babies possible.

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### THE PRACTICAL MANAGEMENT OF SEVERE HYPERTENSION WITH GANGLIONIC BLOCKING AGENTS.

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It is no exaggeration to state that, with the introduction by Paton and Zaimis in 1948 of the methonium type of ganglionic blocking agents, effective medical treatment for severe hypertension has for the first time become available. The potential properties of these compounds in lowering blood pressure are widely recognized, but some doubt still seems to exist as to the practical management of patients who might be suitable for treatment with these drugs. Many physicians still feel that long-term treatment is too complicated and hazardous to be used anywhere except in well-equipped hospitals or special clinics. Such views are held not only in this country; indeed, recently a prominent physician in the United States made the statement that "methonium drugs might be suitable for the stoic British, but would not be tolerated by the average American citizen". It is admitted that treatment with ganglionic blocking agents should not be undertaken by those physicians and patients who are unable or unwilling to spend the time necessary for the meticulous supervision of therapy. The purpose of this paper, however, is to emphasize that it is not only possible to prolong the life of patients suffering from accelerated or malignant hypertension and to relieve them, often dramatically, of distressing symptoms, such as paroxysmal nocturnal dyspnoea and recurrent attacks of pulmonary oedema or failing eyesight due to severe retinopathy, but also that it is possible for patients to return to full occupation. This communication is based on experience in the management of patients treated continuously for up to four years, partly in private practice and partly in the out-patient department of a public hospital. It is hoped to confirm that such therapy may not only be as life-saving as insulin therapy to the severe diabetic, but also that it is entirely practicable.

#### Indications.

The natural history of hypertension and the problem of evaluation of therapy have been discussed most authoritatively by Professor M. L. Rosenheim in the Oliver-Sharpey Lectures (1954). Whilst proof of the value of ganglionic blocking agents in the treatment of severe and accelerated hypertension is rapidly accumulating, there is as yet no conclusive evidence as to the value of these drugs in benign essential hypertension of mild or even moderate degree.

All the patients in this series had one or more of the following indications: (i) accelerated or malignant hypertension with severe retinopathy (grade III or grade IV); (ii) true hypertensive symptoms, especially those of left ventricular failure, paroxysmal nocturnal dyspnoea and recurrent pulmonary oedema; (iii) rising diastolic pressure of 130 millimetres of mercury or more in young subjects, especially males. The only modification, compared with views expressed some years ago (Bauer, 1953), is that symptoms of hypertensive heart failure are now recognized as indications for the use of ganglionic blocking agents, sometimes even before more orthodox measures, such as the exhibition of digitalis, sodium restriction and the use of mercurial diuretics, have been given a full trial.

#### Technique.

Before treatment is commenced, a comprehensive investigation of the patient is essential, in order to determine the extent of hypertensive cardio-vascular-renal damage, and to establish, if possible, an aetiological diagnosis. A full history and clinical examination, including careful inspection of the ocular fundi, are supplemented by electrocardiography, chest X-ray examination and renal function tests. Nearly all patients in this series were referred for excretion pyelography, and some, in the hope that a removable unilateral renal disorder might be discovered, had a full urological investigation. Many patients had one or more of the pharmacological tests for pheochromocytoma, phenolamine ("Regitine"), after the omission of all hypotensive and sedative drugs for one week, being most commonly used during the last two years.

The majority of patients with severe or accelerated hypertension suitable for ganglionic blocking therapy are now treated by the parenteral administration of pentolinium ("Ansolsen"), which has certain advantages over the older hexamethonium discussed below. The parenteral route is chosen because of the poor and unreliable absorption of these compounds from the gastro-intestinal tract—a fact well recognized in the case of hexamethonium, but almost equally true of pentolinium. Harrington (1953) showed that, after the injection of hexamethonium, over 90% can be recovered from the urine within a few hours, while less than 10% of an oral dose is excreted via the kidneys in twenty-four hours. The earlier claims of much smoother absorption of pentolinium have not been substantiated—a fact confirmed by recent publications from the Mayo Clinic (Birkhead *et alii*, 1954; Gifford *et alii*, 1954). The effects of unpredictable gastro-intestinal absorption of pentolinium, even when this is given with all the necessary precautions, resulting in prolonged hypotension or gastro-intestinal ileus, have been seen repeatedly. The experiences over the last few years have convinced the writer not only of the far greater efficiency of the parenteral route, but also of the fact that, in view of the lower incidence of side effects in therapeutic doses, this mode of administration is much more acceptable to the majority of patients. These views are shared by most British authors (Morrison, 1953; Rosenheim, 1954; Shirley Smith *et alii*, 1954).

During the stabilization period, which in the majority of instances does not take more than seven to ten days, every effort is made to obtain the patient's full cooperation. He is given a simple explanation of the action of these drugs, the effects of parasympathetic blockade and of postural hypotension being stressed. It is firmly believed that pharmacological side-effects, such as dry mouth, difficulty in visual accommodation, and gastro-intestinal upsets, are much less troublesome if the patient is fully aware of what to expect and reassurance is given that in the majority of instances these effects either subside or can

largely be alleviated. With regard to postural hypotension, which some authors have regarded as such a nuisance, patients are encouraged to regard minor symptoms thereof as proof of the continued effectiveness of treatment in lowering blood pressure.

The initial titration dose of pentolinium is usually given intravenously with the patient in the sitting posture. An average dose is two milligrammes of the aqueous solution, unless special circumstances such as incipient renal failure, ischaemic heart disease or cerebral disease demand extra caution. In such cases half or even a quarter of the foregoing dose is given. After five or ten minutes, if no pronounced fall in blood pressure is observed, the patient is asked to rise and remain standing for a few minutes. This change in posture usually leads to a considerable drop in blood pressure accompanied by a sinking feeling and faintness. The patient thus learns to recognize the symptoms of hypotension, and also observes that these are promptly relieved by lying down. This demonstration convinces the patient faster than any amount of lecturing of the importance of the upright posture during ganglionic blocking therapy and of sleeping propped up, preferably with nine-inch blocks under the head of the bed, in order to obtain the maximal drop of blood pressure with the smallest possible dose. However, the magnitude of the response to the initial intravenous injection bears disappointingly little relationship to the ultimate subcutaneous stabilization dose.

A few hours after recovery from the first titration injection, the patient receives a subcutaneous dose of, say, 2.5 milligrammes of pentolinium, often suspended in polyvinyl pyrrolidone solution ("Ansolsen Retard"), the effect of which is to delay drug absorption. Before the injection, the blood pressure is taken with the subject standing and sitting, and half-hourly thereafter. If no satisfactory drop in blood pressure results, the dose is increased by 2.5 milligrammes until at the time of maximal action, commonly one to two hours after injection, the pressure is reduced to normal values, or until hypotensive symptoms appear—whichever occurs first. A decision is then made as to whether two or three daily injections are required, and this depends largely on the duration of action of the drug, the severity of the hypertensive process, and the presence or absence of distressing side-effects. For the majority of patients two injections—for example, at 8 a.m. and 5 p.m.—suffice; but for some, especially young males with accelerated hypertension, three injections, approximately at 8 a.m., 2 p.m. and 8 p.m., are advised. Some patients seem more sensitive to the early morning injection, the dose of which is then slightly reduced. Others, especially those liable to paroxysmal nocturnal dyspnoea, are recommended to give themselves an extra large evening injection. The average maintenance dose varies from 2.5 to 25 milligrammes per injection, although one patient required as much as 87.5 milligrammes in order to obtain a satisfactory drop in pressure.

During maintenance therapy the patient is observed at regular intervals. To determine the effectiveness of a given dose no reliance can be placed on a single blood pressure reading; but the patient must be observed for several hours, the blood pressure again being taken before the injection and half-hourly thereafter, with the patient in the standing and reclining posture. As Professor Rosenheim has stated, "a casual blood pressure reading in the outpatient department or surgery gives little information of value, and often upsets the patient and misleads the doctor" (Rosenheim, 1954). Whilst the effectiveness of therapy can be assumed if a given dose repeatedly lowers the blood pressure to satisfactory levels, the patient can really be regarded as having benefited by treatment only if the periodic reassessment demonstrates symptomatic relief, as well as objective improvement in cardiac function and size, and in retinal appearances, and cessation of progression of other hypertensive complications.

#### Side Effects.

Just as the diabetic patient treated with insulin is taught that certain circumstances will cause hypoglycaemic symp-

toms—for example, severe muscular effort or insufficient or delayed food intake—so the hypertensive patient is warned that drug potentiation will occur whenever there is vasodilatation or excessive salt loss. Common causes of vasodilatation are the ingestion of a large meal or alcohol, exercise, pyrexia or the taking of a hot bath; while excessive salt loss occurs with severe perspiration on hot days, with gastro-intestinal upsets accompanied by vomiting and diarrhoea, and during mercurial diuresis. The recumbent posture generally relieves hypotensive symptoms as promptly as the intake of sugar relieves the symptoms of hypoglycaemia. Drugs, such as methedrine or phenylephrine, have never been found necessary to restore blood pressure.

The pharmacological effects of parasympathetic blockade and their management are well known and have been discussed in detail by Smirk (1953). The ocular side effects of difficulty in accommodation and photophobia usually appear within half an hour to one hour after a subcutaneous dose, and last from one to three hours. They are often effectively relieved by spectacles with positive lenses of one to three dioptres and by avoidance of glare. Dark glasses add to the comfort of the patient. Parasympatheticomimetic drugs, such as eserine or pilocarpine, in the form of eye drops, have not been very successful. Dryness of the mouth due to inhibition of salivary secretion occurs at about the same time as the visual effects. It may be severe enough to cause a painful tongue and dysphagia, necessitating rearrangement of meal times so as not to coincide with the maximal discomfort of these reactions. In rare instances the dryness persists in spite of the sucking of lemons, chewing-gum or peppermint sweets, in which case one or two tablets of carbachol or neostigmin may be helpful. Anorexia and weight loss due to gastro-intestinal mobility and reduced gastric secretion, are occasionally seen. Bladder atony rarely presents a serious problem, but many patients, especially males with prostatic enlargement, find it difficult to micturate for several hours after an injection. Impotence is an almost universal by-product of parasympathetic blockade, and in young male subjects constitutes a serious problem. The only effective remedy appears to be the occasional omission of the evening injection. Constipation and intestinal ileus have not been nearly so troublesome with the parenteral administration of pentolinium as with hexamethonium or with pentolinium given by mouth, and can usually be overcome by the use of laxatives or neostigmin given by mouth. The only patient causing anxiety on this account required an unusually large dose of pentolinium.

A male patient, aged forty-eight years, who had suffered from severe hypertension for at least seven years, had been treated since 1953 with hexamethonium. When he was first examined by the writer in March, 1954, he had left off treatment on account of severe gastro-intestinal side effects. His systolic blood pressure was 260 millimetres of mercury and his diastolic pressure 160 millimetres, and he had bilateral papilloedema, hæmorrhages and exudates, auricular fibrillation, cardiac enlargement, triple rhythm, albuminuria and a blood urea level of 35 milligrammes per 100 millilitres. The stabilization dose of pentolinium had to be gradually increased to 87.5 milligrammes per injection before the standing blood pressure dropped to systolic 170 millimetres of mercury and the diastolic pressure to 100 millimetres. After ten days' treatment he became very constipated, with abdominal distension and vomiting. Treatment was temporarily suspended, and this resulted in relief of the gastro-intestinal symptoms within twenty-four hours. With the addition of 1.25 milligrammes of reserpine per day, 25 milligrammes of pentolinium produced a satisfactory drop in blood pressure, and the patient was discharged from hospital on three such injections per day. He felt very much better and was objectively greatly improved, but after eight weeks developed a severe depressive state necessitating his readmission to hospital, and the administration of scoline-modified electroconvulsive therapy. Although reserpine was suspected of being at least partly responsible for the mental reaction, it was then not safe to omit this drug, especially in view of the occasional reappearance of retinal hæmorrhages which threatened to cause blindness. He continued to be retarded and depressed until December, 1954, when reserpine was finally stopped, as a parenteral dose of 25 milligrammes of pentolinium produced an adequate hypotensive response. His condition is now satisfactorily stabilized with three daily



injections of pentolinium, and he has resumed active business life.

#### Results of Therapy.

The most spectacular results are achieved in the treatment of patients suffering from left ventricular failure with paroxysmal nocturnal dyspnoea and cardiac asthma caused by the accelerated form of hypertension. In addition to symptomatic improvement and increased effort tolerance, there may be disappearance of *pulsus alternans* and triple rhythm, as well as significant reduction in heart size and electrocardiographic restitution towards normal.

A male patient, aged fifty-one years, was first examined in October, 1953. He had been found to be hypertensive fifteen years earlier. During the preceding four months he had suffered from incapacitating morning headaches and repeated episodes of paroxysmal nocturnal dyspnoea and cardiac asthma, culminating in four very distressing attacks during the week prior to commencement of hypotensive therapy.

Examination of the patient revealed him to have a systolic blood pressure of 240 millimetres of mercury, and a diastolic pressure of 140 millimetres, bilateral papilloedema, recent flame-shaped hemorrhages and exudates, left ventricular enlargement with triple rhythm, and albuminuria with fixed specific gravity and a blood urea content of 42 milligrammes per 100 millilitres. Within twenty-four hours of effective therapy, headaches ceased, and during the subsequent twenty months not a single attack of paroxysmal dyspnoea occurred. He is now treated with an early morning injection of 10 milligrammes of pentolinium retard, a midday injection of 10 milligrammes, and an evening injection of 15 milligrammes, in an attempt to keep his blood pressure at safe levels during a large part of the day. Papilloedema disappeared rapidly, triple rhythm is no longer audible, the cardiac size diminished, and an electrocardiogram showed great restitution from the left ventricular strain pattern towards normal. The blood urea level after eighteen months' treatment was 37 milligrammes per 100 millilitres. He left off dietary sodium restriction and digitalis over fifteen months ago, and now leads an active life.

The majority of patients whose blood pressure is satisfactorily stabilized can be treated without additional sodium restriction, mercurial diuretics, or digitalis, even though these were essential prior to hypotensive therapy. However, in view of the rare occurrence of lung changes during methonium therapy (Doniach *et alii*, 1954), some authorities prefer to continue the administration of digitalis, on the assumption that it might prevent the development of this complication (McMichael, 1954).

In cases of accelerated hypertension with visual disturbances due to retinopathy, successful therapy may restore normal eyesight.

A male patient, aged twenty-six years, presented in May, 1953, on account of a six weeks' history of blurred vision. On examination he was found to suffer from accelerated hypertension with a blood pressure of 270 millimetres of mercury, systolic, and 170 millimetres, diastolic; bilateral papilloedema, flame-shaped hemorrhages and recent exudates and a macular star, triple rhythm and albuminuria were also present. In spite of extensive investigations no cause for the hypertension was discovered, and he was treated with three injections of 110 milligrammes of hexamethonium bromide. There was rapid decrease in the retinopathy, the triple rhythm disappeared and the electrocardiographic changes of left ventricular hypertrophy regressed. During the following year he continued to work hard as a butcher, his condition being satisfactorily controlled until October, 1954, when, tired of putting up with daily injections, he demanded a trial with pentolinium given by mouth and reserpine. His blood pressure response to this regime was inadequate, and when he was examined in February, 1955, he complained of headaches; his systolic blood pressure was 250 millimetres of mercury and his diastolic pressure 180 millimetres, and frank papilloedema and numerous recent hemorrhages were visible. A loud triple rhythm was heard again, there was considerable deterioration in the electrocardiogram, and the blood urea level had risen in the four months from 41 to 58 milligrammes per 100 millilitres. His blood pressure was subsequently restabilized with pentolinium given parentally, and it will be interesting to see whether a second remission can be induced.

The evaluation of headache in hypertension is notoriously difficult, but if this symptom is of incapacitating severity and resistant to all other forms of treatment, a trial with ganglionic blocking agents may give most gratifying results.

A male patient, aged fifty-four years, was suffering from essential hypertension of seven years' duration, with severe migraine-like paroxysms of headache and tinnitus of increasing severity. The systolic blood pressure was 220 millimetres of mercury and the diastolic pressure 130 millimetres, and examination of the optic fundi revealed narrowed arterioles but no hemorrhages, exudates or papilloedema. Blood pressure reduction was satisfactorily instituted in August, 1954, with two daily injections of 3.75 milligrammes of pentolinium retard, supplemented by a midday oral dose of 100 milligrammes. During the subsequent ten months he has hardly had a headache and tinnitus has disappeared completely. There has been concomitant improvement in the fundal appearance and in the electrocardiogram.

The onset of the accelerated phase may be heralded by frank haematuria, and, provided that this is recognized as an urgent indication for the administration of hypotensive agents, the results are again quite spectacular.

A male patient, aged forty-five years, was first examined in October, 1953, on account of haematemesis and melena due to a bleeding duodenal ulcer. Examination at that time, after restoration of blood volume, showed him to have a systolic blood pressure of 210 millimetres of mercury and a diastolic pressure of 140 millimetres, and considerable narrowing of arterioles with venous nipping, but no papilloedema, hemorrhages or exudates. He was examined again in March, 1954, presenting with frank haematuria, severe headache, and early left ventricular failure. His systolic blood pressure was 230 millimetres of mercury, and his diastolic pressure 150 millimetres, and examination of the fundi revealed early bilateral papilloedema with recent flame-shaped hemorrhages and cotton-wool exudates; the blood urea level had risen from 21 to 40 milligrammes per 100 millilitres. He was satisfactorily treated with three daily injections of pentolinium retard, at first five milligrammes per injection, the dose being later adjusted to 10 milligrammes. During the past fifteen months he has had no further haematuria or headaches, and apart from the improvement in the appearance of the ocular fundi and the electrocardiogram, there has been an increase in his effort tolerance which has allowed him to resume his profession as full-time university lecturer.

#### Relative Contraindications.

It is well recognized that extra caution is required in the presence of renal failure, coronary disease or cerebral vascular disease. In renal failure, as indicated by a blood urea level of over 100 milligrammes per 100 millilitres, pentolinium may further reduce glomerular filtration rate and effective renal plasma flow. However, if other indications for blood pressure reduction are urgent, such as episodes of severe left ventricular failure or rapidly progressive retinopathy with threatened blindness, and provided that the patient is not frankly uraemic, cautious therapy, commencing with such small doses as 0.5 milligramme of pentolinium, is justified. The life expectancy of such patients is very limited, but every now and again a worthwhile remission may be obtained.

A female patient, aged twenty-seven years, was first examined in November, 1953, on account of severe breathlessness. Her systolic blood pressure was 250 millimetres of mercury and her diastolic pressure 160 millimetres, and she had bilateral papilloedema, gross left ventricular enlargement, albuminuria and a blood urea level of 133 milligrammes per 100 millilitres. In view of the rapidly progressive symptoms of hypertensive heart failure, it was decided to institute blood pressure reduction, in spite of the renal failure. She was treated at first rather unsatisfactorily with pentolinium given by mouth in a dosage varying from 60 to 120 milligrammes three times a day, her condition swinging from severe hypotensive reactions to periods of inadequate control. In September, 1954, the regime was changed to two daily injections of 7.5 milligrammes of pentolinium retard. Until April, 1955, she continued full-time work as a telephonist. In May, 1955 she was readmitted to hospital and died of uraemia, eighteen months after the diagnosis of malignant hypertension due to chronic glomerulo-nephritis had been made.

In view of the delayed renal excretion of methonium in the presence of renal failure, precautions must be taken to avoid cumulative effects, and cases have been encountered in which each injection lowers the blood pressure for forty-eight to seventy-two hours.

In cardiac infarction hypotensive therapy is contraindicated for a rather arbitrary period of six weeks.

Patients liable to anginal pain sometimes experience chest discomfort at the time of maximal drug action, which is relieved by trinitrin used in the usual manner, and also by raising the blood pressure. Although at first these attacks caused considerable alarm, further experience showed that these ischemic episodes tended to disappear after a few days. Similar symptoms, referable to the cerebral circulation, may be observed with transitory paræsthesiæ or muscular weakness. Shirley Smith (1954) reported the case of a patient who developed temporary dysphasia after every injection. Whilst caution is undoubtedly necessary, failure to institute effective therapy can be equally disastrous.

A male patient, aged forty-five years, who had been severely hypertensive for seven years, had a bilateral sympathectomy performed in 1948, with a good temporary result. In August, 1954, he began to experience increasingly severe anginal pain, his systolic blood pressure then being 210 millimetres of mercury and his diastolic pressure 135 millimetres, and cardiac enlargement and early left ventricular failure were also present. Examination of his ocular fundi revealed arteriolar narrowing, but no papilloedema, hæmorrhages or exudates. The need to lower blood pressure was recognized, but in view of the severe anginal symptoms, impending cardiac infarction was diagnosed and the patient was put to bed for a fortnight. On the twelfth day the patient experienced further severe chest pain, without the electrocardiographic changes of recent infarction. He was transferred to hospital, but within a few hours of admission and before the institution of any therapy he suddenly expired. Autopsy showed that he had died from a massive cerebral hæmorrhage.

Although isolated reports of cardiac and cerebral infarction during hypotension have appeared in the literature, in very few is the evidence incriminating such therapy really convincing. The fluctuations of blood pressure induced by the parenteral exhibition of ganglionic blocking agents have never been shown to be harmful—indeed, the risks of continued high pressure far exceed the possible dangers of a sudden fall in pressure, a point well exemplified by the foregoing case report.

Patients with widespread cerebral vascular degeneration and early mental changes are on the whole not suitable for methonium therapy. Although their cardiac status may improve, the mental symptoms are often adversely affected, quite apart from the often insurmountable difficulty of adequately supervising treatment under such circumstances.

#### Comparison of Hypotensive Agents.

Of the ganglionic blocking agents currently available, pentolinium has certain advantages over hexamethonium. Firstly, since it is five times as potent, the effective dose is much smaller than that of hexamethonium. Secondly, a subcutaneous dose of pentolinium, both aqueous and in polyvinylpyrrolidone solution, acts for one to four hours longer than hexamethonium in a similar solution. Thirdly, drug tolerance, which is almost universal with hexamethonium during the first two to four weeks of treatment, is not nearly so frequent with pentolinium; indeed, many patients require reduction in dosage rather than increase with prolonged therapy. Fourthly, side effects, with the exception of visual disturbances, are less troublesome with pentolinium; especially are gastro-intestinal upsets less severe.

Whilst a general preference has been expressed for the parenteral administration of pentolinium in the treatment of severe and accelerated hypertension, it is not intended to convey the impression that its oral administration has no place in therapy at all. However, experience has shown that generally only those patients suffering from less severe forms of hypertension, and those who obtain satisfactory blood pressure control with five milligrammes of pentolinium or less given parenterally, get worthwhile results with tablets. Some of these cases belong to the more benign category of hypertension and do not satisfy the criteria for ganglionic blocking therapy enumerated above.

Before this section is concluded, a short comparison of pentolinium with other hypotensive agents now available and discussion of the problem of combination therapy may

be useful. At the present moment rauwolfia preparations, as extracts of the whole root of *Rauwolfia serpentina* or as the alseroxylin fraction, or as the pure alkaloid reserpine, are enjoying great popularity. As mild hypotensive agents with a potent tranquillizing action, they fill an important therapeutic gap, especially in the management of the tense hypertensive in the early labile phase. Though occasionally good results are seen even in severe cases, the response generally, when assessed on objective findings, is disappointing, and at the best the place of rauwolfia in the therapy of such patients is being defined as an adjunct to the more potent ganglionic blocking agents. It is also necessary to stress that rauwolfia, given in doses exceeding one milligramme per day over a prolonged period, is by no means free from undesirable side effects, being especially apt to induce mental depression. Hydralazine compounds, whilst possessing hypotensive properties, are potentially toxic; at the commencement of therapy severe histamine-like headache is common, whilst prolonged administration may lead to the development of a syndrome resembling disseminated lupus erythematosus. The usefulness of veratrum preparations is severely limited by their gastro-intestinal toxicity, which is hardly reduced by the introduction of pure alkaloids. Even the results as given in favourable reports, such as that of Currrens *et alii* (1953), do not compare well with those achieved by ganglionic blocking agents. Dihydrogenated ergot derivatives enjoyed only a short vogue of popularity, and in view of their very feeble hypotensive action they are again lapsing into obscurity. It is not intended to discuss surgery, except to mention that since the introduction of effective drug therapy the number of sympathectomies performed for hypertension has been drastically reduced, this being especially due to the unpredictability of results and the high operative morbidity. Total adrenalectomy for hypertension has not passed the experimental stage and does not seem likely to do so.

Various combinations of the above-mentioned drugs, with or without ganglionic blocking agents, have been advocated. Obviously some time must elapse before critical evaluation and comparison of these methods become possible. However, in most cases of severe or accelerated hypertension, the parenteral administration of ganglionic blocking agents will do all that these "combination cocktails" can achieve, without the further complication of multiple dosage adjustment and toxicity.

The search for better hypotensive agents continues with great intensity in many laboratories, and several new compounds have already been made available for clinical trials. There is justification for the hope that improved preparations will soon become available for our patients.

#### Summary.

Hypertensive cardio-vascular disease ranges in severity from the mild form, requiring nothing more than sympathetic reassurance and periodic supervision, to the grave accelerated or malignant type carrying a very serious prognosis. Medical treatment of patients in the latter group has become possible and practicable with the introduction of ganglionic blocking agents. Case selection, technique of blood pressure stabilization and maintenance therapy by the parenteral administration of pentolinium are discussed, and favourable results, especially in patients with left ventricular failure and visual disturbances due to retinopathy, are reported.

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### CONCERNING PANCREATITIS.

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PANCREATITIS is a fashionable disease, and this, as always, results in an increased volume of literature and reports of a greater number of cases. It also results in confusion of nomenclature, classification and treatment.

The increasing recognition of this frequent disease may be attributed to the following: (i) Zollinger's experiment on the site of pancreatic pain, (ii) Somogyi's improved amylase tests, (iii) the appreciation of tenderness over the pancreatic tail.

Zollinger implanted electrodes into the head, body and tail of the pancreas of patients undergoing biliary surgery. Subsequent stimulation produced pain as follows: head electrode, right hypochondriac pain; body electrode, epigastric pain; tail electrode, left hypochondriac pain; all electrodes, band-like pain passing into the back.

The fact that these types of pain may be pancreatic and yet be indistinguishable from other lesions causing pain in these sites throws the onus of diagnosis on the eliciting of tenderness over the pancreatic tail and on the serum amylase estimation. It is remarkable how often these two features may be indicative of pancreatitis before operations on the gall-bladder, and the explanation of the "post-cholecystectomy syndrome" is rapidly forthcoming in this event. On the other hand, the presence of a peptic ulcer penetrating the pancreas may be divulged by the pancreatitis induced, and the ulcer having been missed on X-ray examination with a barium meal, may confront a surprised surgeon at laparotomy.

When a recent series of 50 cases of pancreatitis was being reviewed it was evident that the Somogyi method of estimating the serum amylase content was much more sensitive than other methods, apparently because it is based on glucose estimation instead of on starch. It is much more consistent with the clinical findings and the response to therapy. The amylase investigation is very important in the confirmation of the diagnosis, and a standard method yielding reliable results is urgently required. The biochemical methods employed appear to me, in many instances, to leave much to be desired.

These further points remain to be stressed. Pancreatic pain, if severe, persists for more than the day as a rule, which differentiates it from biliary colic, and during this period the serum amylase level is raised, even though the symptoms are abating.

Pancreatitis may so readily be confused with, or indeed be accompanied by, biliary disease, peptic ulcer (penetrating) and hiatus hernia that these considerations are important. It is worthy of mention here, too, that upper abdominal dyspepsia and pain with pronounced menstrual

and psychosomatic fluctuation, or with dietary and alcoholic aggravation, should always suggest pancreatitis.

### Pathogenesis.

Whenever the cause of a condition is conjectural, discussions on its pathology often generate more heat than light.

Functional and psychosomatic states commonly accompany pancreatitis. The evaluation of the functional element is difficult when an organic basis coexists. What is equally important is that improper surgery aggravates the psychic disability. It is imperative to procure prompt alleviation of symptoms by any radical surgery on the pancreas.

There appear to be three factors which determine the clinico-pathological course of the disease: (i) necrosis, (ii) exudation, (iii) obstruction. The clinical features most reliably indicate the extent to which these factors are operating.

### Necrosis.

The degree of shock is the best index of the degree of pancreatic necrosis. Necrosis is the most lethal factor in pancreatitis, and it may even be associated with sudden death. The cause of pancreatic necrosis is the escape of the highly proteolytic pancreatic juice from the acini.

Two important elements are here concerned. Firstly, the proteolytic juice is of "nervous" (hypothalamic) origin, and is concentrated and very rich in enzymes (thus differing considerably from its complementary substrate, the duodenal juice, which is watery, profuse and poor in enzymes). Secondly, the essential factor is the rupture of the acini, for it is this catastrophe which releases the tide of disaster. Alan Thal has shown that bile reflux in the pancreatic duct has no vascular effect unless the intraductal pressure is so high as to produce ductal rupture. He has also shown that ischaemia is the basic element in this rupture and may be produced in several ways (Schwartzmann phenomenon, specific protein sensitization *et cetera*). The lesion is fibrin-platelet, capillary and venular thrombosis.

This forward step does not completely satisfy the clinician, who sees in the frequency of postoperative pancreatitis (even after eye operations) the phenomena of the reaction of the body to stress, and expects that an ultimate hormonal cause will explain this penultimate ischaemia.

In this regard it is of interest to refer to the disturbances of the "health-disease balance" of the abdominal tissues, which is also involved in many common and obscure diseases (peptic ulcer, appendicitis, gall-stones and non-specific enterocolitis of all types, including the Crohn's and ulcerative varieties). It is not unreasonable to hope that the solution of one of these problems will institute a new era in the pathology of abdominal disease comparable with the impact of Listerism on surgery.

Two other physical signs deserve the attention of the clinician: (a) Tenderness in the iliac fossae, with or without abdominal rigidity, may be used as an index of the degree of fat necrosis and intraperitoneal exudation. (b) Ileus may be used with advantage as an index of the degree of retroperitoneal effusion. If it is associated with oligæmic shock, this effusion is usually blood, and the outlook is grave.

Resuscitation from shock is imperative and requires the same courage and enterprise as in burns. The first prerequisite to recovery is adequate transfusion. In certain of these cases the condition is early irreversible and the patients are resistant to resuscitation. Neither do they respond to cortisone or to noradrenaline, which indicates that other factors than adrenal failure are present.

In my opinion, thiouracil (200 milligrammes three times a day at intervals of six hours) by mouth is also justified when the patient is recovering, but apart from this the stomach should be kept empty and all feeding should proceed parenterally. At this stage the use of hexa-



methonium bromide in one of its various forms should be commenced, and it should be continued until oral feeding is well established.

It is not rare to find that despite adequate resuscitation the patient fails to improve. There are four common causes for this dilemma: (a) The degree of pancreatic destruction is so advanced that death is inevitable. (b) Hypocalcaemia is present. A blood calcium estimation should always be carried out, and any deficiency corrected by the intravenous administration of calcium gluconate solution. (c) Infection has supervened in the necrotic pancreas. Pancreatic abscess is a difficult condition to prevent, more difficult to recognize, and most difficult to treat, as one is never sure when surgery should be urged. The heavy exhibition of antibiotics is imperative in all cases of necrotic pancreatitis (and this includes traumatic cases). In my experience the most helpful investigations are the rising leucocyte count and sustained blood sedimentation rate. I have also been assisted on more than one occasion by duodenal deformity demonstrated by X rays with a small barium meal during its passage through the duodenum. I favour early surgery when the condition has become apparent. (d) A pseudocyst has formed. Unless the cyst has become infected, operation should be deferred until the patient is fit. The possibility of malignant disease should always be kept in mind, so that an intended cyst drainage may at laparotomy be transformed into a total pancreatectomy—and a difficult one at that. There is much controversy regarding the best methods of cyst drainage, and each proponent defends his favourite procedure with vigour. At the moment the advocates of the *Roux-en-Y* method appear to have the upper hand; but I have had no reason to abandon internal drainage into the loop of upper jejunal segment isolated by entero-anastomosis.

It will be obvious from these remarks that there is no urgent surgery of the pancreas. Diagnostic laparotomy should not be confused with pancreatic surgery, for it does not permit of deliberate pancreatic operations. Indeed, in the modern view, laparotomy increases tenfold the death rate in acute pancreatitis (McNeill Love) and is therefore a grave diagnostic and judicial error. It would appear to be avoidable if facilities for the Somogyi amylase estimation were available at all times and in all acute abdominal conditions.

#### Exudation.

If necrosis (apart from fat necrosis) is not present, recovery is the rule. Pain is the outstanding feature of these cases, and is usually classical and associated with tenderness over the pancreas. The attack most frequently persists for a few days, during the early phase of which the serum amylase level is raised. Certain cases are due to trauma at operation (as in gastrectomy or operations on the lower bile duct), others to pancreatic penetration by a peptic ulcer. If these two causes may be excluded, the element of obstruction (see below) is the common cause, combined with exudation, to produce subacute pancreatitis, which is often recurrent. The exudate is pancreatic juice with a low enzyme content, but profuse in quantity. It is mingled with oedema fluid, and its stimulation is effected by "secretin", a duodenal enzyme. It is for this reason that if the stomach is kept empty during the active phase and gastro-duodenal secretion is suppressed by the use of hexamethonium bromide, the duodenal hormone is kept in abeyance and resolution usually follows. It should be emphasized that resolution is the outcome in the majority of the cases, and that early intervention in these cases is therefore not warranted. Moreover, in more than half the cases there is no recurrence, so that a conservative attitude should always be adopted even in the presence of one or two recurrent attacks.

Various opinions are expressed in the literature concerning the concomitant existence of gall-bladder disease. In my view it is almost universal, and I have been very impressed with the presence of "strawberry gall-bladder" or early opacity of the cholecystic wall at operation on these patients, despite disarming X-ray reports before the undertaking. This much is worthy of discussion—that

before any operation on the gall-bladder or bile ducts is contemplated the patient should be closely examined by the clinician to elicit the following abnormalities: (i) the presence of left-sided pain during the episodes; (ii) a history of prolonged attacks (more than one day); (iii) any evidence of left-sided tenderness over the pancreatic tail. In the event of any or all of these features being in existence, the serum amylase estimation should be performed. A negative finding does not overshadow the clinical impression. There should be considerable hesitation in performing cholecystectomy in the absence of stones or colic if these features are suggested. The post-cholecystectomy syndrome, in my opinion, is so often pancreatic (or ampullary) in origin that the post-operative course and prognosis may be very different if the possibility of these conditions is kept in mind before the resort to surgery.

Further, when cholecystectomy is contemplated and when the cause of the dyspepsia is indicated only by a non-filling organ on cholecystographic examination, it is wise to proceed warily if the dyspepsia is aggravated by the menses, by a psychical crisis, by an alcoholic "bender" or by any injury, including surgery. These incidents are very suggestive of pancreatitis. The patient who has recently undergone cholecystectomy, and whose symptoms are now the same as or worse than before operation, is not inspired with confidence in his surgeon. Far from being an operation to be undertaken by the occasional surgeon, bolstered with a confirmatory result to Graham's test, cholecystectomy is an operation upon which more than one surgical reputation has been undone.

I am always at some pains to determine whether the ampulla of the common bile duct is affected. The use of intravenous "Biligrain" choledochography is a modern aid, but it has not supplanted the careful and repeated examination of the urine in these cases for the presence of bile. Intermittent billuria remains the best index of lower ductal involvement before overt obstructive jaundice occurs.

#### Obstruction.

There now exists an increasing school of clinicians who believe that the element of obstruction is of as great importance in the pancreato-biliary system as it is in the urinary system. The infective theory of cholecystitis is regarded with suspicion, and the fibrotic obstruction which affects the gall-bladder, the ampulla of the common bile duct, the liver and the pancreas is believed to be of metabolic (hormonal) origin.

In the pancreas, obstruction affects (a) the orifice of the pancreatic duct, (b) the main duct (leading to stone formation), (c) a lobule (leading to fibrotic nodules in the gland). Official obstruction of the duct is often associated with benign fibrosis of the ampulla of the common bile duct and with gall-bladder disease. I have now operated upon 19 patients since 1948. I failed to find the duct orifice in three cases (owing to oedema or phlegmon). In the remaining 16 cases, one patient, aged sixty-two years, required sympathectomy for subsequent recurrence, one complains of unexplained vomiting without pain, while two continue to complain of mild pain requiring dietary restriction. Most of these patients are aged over forty years.

The remaining twelve patients are cured and symptomless. In my series this operation is superior to sphincterotomy alone. It would appear that the reversibility of the pancreatic disease is the basic factor in the prognosis.

It is for this reason that the attack on the duct, in my opinion, is not to be recommended when either phlegmon or fibrosis is pronounced, or for the older patient with a long history of pancreatic and biliary disease. When phlegmon is present, the patients appear to do well with pancreato-duodenal resection. Phlegmon should be suspected (i) if the symptoms abate slowly after a recent attack, (ii) if the pancreas remains tender (or palpable), (iii) if the plain X-ray film of the abdomen reveals a dilated duodeno-jejunal segment of the gut, (iv) if the

serum amylase level remains high, (v) if there is evidence of obstructive jaundice.

In my view, the best index of fibrosis is steatorrhœa. Examination of a smear of the stool treated with acetic acid and stained with one of the fat stains (Sudan III) will reveal many fat globules.

Pancreatic ductal disease does not appear to be an isolated entity, and there usually coexists fibrosis of the lower end of the common duct and gall-bladder disease. Even when the results of pre-operative tests have acquitted these structures, abnormality is often divulged at laparotomy. Therefore, failure to deal with these conditions may invalidate the primary operation on the duct orifice.

When the disease affects a lobule the resulting lesion has proved misleading to me during the search for an islet-celled tumour.

Involvement of the main duct decides the site of ductal obstruction. At that site a stone may form. If other stones subsequently form, this stone remains the largest or "lead" stone. Removal of the stone and provision of free drainage, either by dilating the duct to the orifice or by short-circuiting the duct at its widest part into the adjacent stomach or duodenum, is advisable if the pancreatic fibrosis is moderately severe (that is, if the pancreas is not shrunken). The fibrosed, shrunken, painful gland is, in my experience, best dealt with either by repeated injection of the celiac ganglion or by sympathectomy. Pancreatic resection in these cases is not followed by a completely cured patient and is therefore not justified.

It is my practice to inject the celiac ganglion, under intravenous morphine narcosis, with about 10 cubic centimetres of 2% "Xylocaine" solution, followed immediately by two to five cubic centimetres of "Efocaine" or its equivalent. This procedure is often sufficient in cases of moderate degree and may be repeated; but for the severe cases sympathectomy (from the tenth thoracic to the second lumbar ganglia with splanchnic nerve resection), either unilateral (on the side of the pain) or bilateral, is indicated.

#### The Role of Surgery.

Surgery in pancreatitis will probably be required under the following conditions:

1. For associated conditions of the gall-bladder and bile duct.
2. For failure to recover from the acute attack: (a) in cyst formation associated with infection and necrosis or with malignant disease; (b) in abscess formation. In these conditions pancreatic fistula may develop and require anastomosis of the duct to an adjacent viscus (usually the stomach).
3. For painful fibrosis requiring celiac injection or sympathectomy.
4. For phlegmon. Persistent phlegmon appears to respond well to resection.
5. For ductal stricture: (a) orificial stricture in young patients with severe recurrent pancreatitis; (b) ductal stricture with stones.
6. For malignant change.

#### Summary.

1. Better diagnosis and increased interest in pancreatitis are resulting in the recognition of more cases and are bringing into prominence our ignorance of causation and treatment.
2. Pancreatitis is commonly associated with other abdominal and psychosomatic states, and careful evaluation is necessary.
3. Various forms of treatment are applicable, depending on the clinical assessment of the pathogenetic factors which are present in each patient.
4. The indications for these various therapies are discussed.

## Reviews.

**The Diabetic Life: Its Control by Diet and Insulin: A Concise Practical Manual for Practitioners and Patients.** By R. D. Lawrence, M.A., M.D., F.R.C.P. (London); Fifteenth Edition; 1955. London: J. and A. Churchill, Limited. 8½" x 5½", pp. 240, with 19 illustrations. Price: 12s. 6d.

A FURTHER EDITION of R. D. Lawrence's "Diabetic Life" brings in the fifteenth edition of this popular manual in thirty years. His object of "... a simple and practical guide on the treatment of diabetes, with theory kept to a minimum" is fully realized. The "Line Ration" diet is preserved, but has been liberalized to contain more "black" (carbohydrate) lines than "red" (protein and fat) lines, but detailed diets and recipes have been omitted. There is a full description of the new "Lente" insulins which are advocated for new patients requiring insulin, rather than for patients whose condition is already stabilized on the older mixtures. Dr. Lawrence confesses that he uses his simple unweighed diet quite freely nowadays. His preference for the insulin zinc suspension is largely due to the possibility of limiting the number of injections to one per day. His complaint that there are now too many insulins (seven on the British market) will be agreed to by most practitioners. In our experience "semi-lente" (amorphous) insulin has its maximum effect well short of the ten hours claimed by the author. The irregularity of action of protamine zinc insulin is shared also by lente insulin, and must surely depend upon uneven absorption from various local sites. A little more may perhaps have been said on the subject of "steroid diabetes", which is such a constant threat to patients on long-term cortisone therapy. Dr. Lawrence gives no support to the adherents of "free diet" régimes, and concludes that constant hyperglycemia is harmful. He prefers to see a small amount of glycosuria than to hear patients complain of frequent hypoglycemia. A further principle in patient education is also stressed, namely, the most desirable time to test the urine, dependent upon the type and dose of insulin in use. The initial dose of insulin recommended for the treatment of pre-coma is 40 units, to be repeated in four hours, and no large initial dose is given for the patient in complete coma. This dosage level is less than half that in common use elsewhere. Dr. Lawrence wisely advises the admission to fully equipped institutions of all patients in pre-coma and coma. Reference is made to the direct degeneration first of non-medullated and later of medullated nerve fibres as the true pathological characteristic of diabetic neuritis, rather than to disease of the *vasa nervorum*, and to the futility of treatment by vitamins. In pregnancy, no final statement is made in regard to the value or otherwise of estrogens. The interesting subject of the prediabetic state is not discussed, nor is mention made of the question of blood insulin to which Dr. Lawrence has made an important contribution.

This manual is really for the doctor, and contains all that a general physician or practitioner needs to know in order to treat any diabetic with success. It remains the best manual available among many, and embodies forty years' experience of a diabetic among diabetics. It is conservative, practical and easy to understand.

**Practice of Allergy.** By Warren T. Vaughan, M.D., revised by J. Harvey Black, M.D.; Third Edition; 1954. St. Louis: The C. V. Mosby Company. Melbourne: W. Ramsay (Surgical), Limited. 10" x 7", pp. 1184, with 335 illustrations. Price: £11.

THE third edition of this book (revised by J. H. Black) shows many of the characteristics noted in our review of the second edition published in this journal in 1949. In his preface Dr. Black comments on the slow progress in knowledge of the allergic diseases in spite of the increasingly great mass of relevant literature, and, although he has 57 closely printed pages of references, he confesses that he has had to omit many worthwhile papers. To digest and clearly summarize this mass presents an almost impossible task, and, although the experienced specialist will find interest in almost every page, the beginner with little experience may find it difficult, at times, to obtain precise guidance on some of his problems. For instance, penicillin sensitivity is mentioned, but no precise directions are given on methods of testing for allergy to it, nor is any personal opinion given as to whether or not the tests are dependable. The chapter on preparation of test extracts is, in part, out of date. The fact that there is no really satisfactory method of standardizing the potency of extracts is mentioned, and then follows a rather weak recommendation that extracts should be standardized by estimation of either the total or

protein nitrogen. The labelling of extracts with fictitious units has led to trouble in the past. Notwithstanding these minor criticisms, this text-book contains a large amount of very useful information attractively presented. Chapters of especial interest are those on the history of the study of allergic diseases, on pollen surveys and on tests of pulmonary function. The printing, format and illustrations are excellent.

**Outline of Law in Australia.** By John Baalman; Second Edition; 1955. Sydney: The Law Book Company of Australasia Proprietary, Limited. 8½" x 5½", pp. 310. Price: 25s.

SINCE "Outline of Law in Australia", by John Baalman, was first published in 1946, important decisions by the Courts and significant legislation have justified a second edition of this valuable work. The addition of entirely new sections, the amendment of the earlier text to accord with recent changes in the law and the expansion and bringing up to date of the bibliography will make it worth while for those acquainted with the first edition to study its successor.

The work is described as being for "those members of the community who, without any intention of adopting law as a profession, regard some knowledge of the rules which regulate their daily conduct as a sheer cultural necessity".

Its outstanding characteristics are the effectiveness with which it encompasses in a small space the more important doctrines of a complex and vast subject, the clarity of the treatment of technical themes and the cultivated and vital style of writing. For the most part the apportionment of space to the relative importance of a particular topic is well considered, but now and again matters get a little out of balance. It is understandable that the author, who has long been concerned with the work of the Law Titles Office, should pay particular regard to such matters as the law of property with its origins in feudal tenures. In view of the title of the book, however, it seems unfortunate that taxation law should not receive some emphasis. The operation of the Federal Constitution and, in particular, the implications of Section 92 are of great importance, yet the latter is not analysed, whilst the whole of the Constitutional field receives little more of the text than does "Title by Adverse Possession". One should not forget, however, the following just observation by the author himself in the preface: "In composing a work of this nature there was a major difficulty in deciding not what to put in it, but what to leave out. The subject of law is so vast that the pruning knife had to be used ruthlessly."

Of the new material introduced to the second edition, the sections on workers' compensation, citizenship, and arbitration are of special interest.

**Doctor Against Witchdoctor.** By E. W. Doell, with illustrations by Con Purchase; 1955. London: Christopher Johnson. 8½" x 5½", pp. 216, with many illustrations. Price: 15s.

This collection of tales and reminiscences tells of the struggles of a doctor to help African natives in spite of the sinister grip their witch-doctors have on them. It depicts, obviously with veracity, and with sincerity and sympathy, the unending frustration of the battle against superstition and suffering. Medically it contributes nothing of value, but the simplicity of the presentation of its theme is appealing.

**The Shoulder and Environs.** By James E. Bateman, M.D., F.R.C.S.(C.); 1955. St. Louis: The C. V. Mosby Company. Melbourne: W. Ramsay (Surgical), Limited. 10" x 7", pp. 566, with 376 illustrations. Price: £8 10s. 9d.

This is a very good book and a very complete one. In it the author has presented a new approach to the problem of diagnosis of shoulder disease. Disorders of the shoulder girdle are divided into three categories: (a) disorders with shoulder neck pain; (b) disorders with shoulder pain predominating; (c) conditions producing shoulder pain plus radiating pain. This classification is highly successful and is well and thoroughly developed by the author. In addition there are very good chapters on "Nerve Injuries and Paralytic Disorders about the Shoulder" and "Fractures and Dislocations of the Shoulder Region".

There is no doubt that the author has a message to the profession, but it is felt that in his effort to achieve completeness, he has made his vehicle rather too large. His message seems to be to the already well qualified, and for them 150 pages devoted to the embryology, the anatomy, the physiology and the examination of the shoulder is perhaps too much. Fifty pages also are devoted to "Tumours of the Shoulder Region", but these, naturally, are not confined to

the shoulder girdle and occur elsewhere in the body with equal frequency, and it is thought that, in a work of this nature, this chapter is rather unnecessary.

The book is beautifully produced and lavishly illustrated with many excellent photographs, X-ray pictures and diagrams which add to its undoubted excellence. Where there is so much to praise, it is perhaps carping to criticize, but we think that had the message been delivered in a less bulky package it would achieve a wider circulation and a greater popularity.

## Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Ciba Foundation Colloquia on Ageing. Volume I: General Aspects", edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Margaret P. Cameron, M.A., A.B.L.S., assisted by Joan Etherington; 1955. London: J. and A. Churchill, Limited. 8" x 5½", pp. 270, with 38 illustrations. Price: 30s.

Seventeen subjects are dealt with; there are discussions, some on a single subject and some on groups of subjects.

"World Distribution of Sprochetal Diseases. 1: Yaws, Pinta, Bejel: Basic Sources", by the Department of Medical Geography, American Geographical Society; 1955. New York: American Geographical Society. 38" x 25". Price: \$1.25 folded, \$1.50 flat.

The map shows the disease distribution and the basic sources of information are stated.

"Annual Epidemiological and Vital Statistics, 1952"; 1955. Geneva: World Health Organization. 11" x 8½", pp. 544. Price: £2 10s.

Comprises 73 statistical tables "which provide an extensive and varied picture of the demographic and health situation" for 1952 in various countries.

"Medical and Public Health Laboratory Methods: Successor to Fifth Edition of Laboratory Methods of the United States Army", edited by James Stevens Simmons, S.B., M.D., Ph.D., Dr.P.H., S.D.(Hon.), and Cleon J. Gentzkow, M.D., Ph.D.; 1955. Philadelphia: Lea and Febiger. Sydney: Angus and Robertson, Limited. 9½" x 6", pp. 1192, with 115 illustrations and nine colour plates. Price: £10 3s. 6d.

There are 35 contributors. The book comprises eleven parts and is divided into 52 chapters.

"Proctologic Anatomy", by R. V. Gorsch, A.B., M.D., F.I.C.S., F.A.P.S., D.A.B.P.; Second Edition; 1955. Baltimore: The Williams and Wilkins Company. Sydney: Angus and Robertson, Limited. 9" x 6", pp. 326, with 155 illustrations. Price: 88s.

The author's object is "to present a comprehensive and simple description" of essential perineo-pelvic anatomy. He is a clinical professor of proctology.

"A Primer of Electrocardiography", by George E. Burch, M.D., F.A.C.P., and Travis Winsor, M.D., F.A.C.P.; Third Edition; 1955. Philadelphia: Lea and Febiger. Sydney: Angus and Robertson, Limited. 9" x 6", pp. 286, with 281 illustrations. Price: 55s.

The first edition was published in 1945.

"Statistics of Therapeutic Trials", by G. Herdan, M.Sc., Ph.D., LL.D.; 1955. Amsterdam, Houston, London and New York: Elsevier Publishing Company. London: Cleaver-Hume Press, Limited. 9" x 6", pp. 384, with 80 illustrations. Price: 50s.

The author has adopted a medical instead of a mathematical approach to the subject.

"The Interpretation of Dreams", by Sigmund Freud; translated from the German and edited by James Strachey; 1954. London: George Allen and Unwin, Limited. 8½" x 5½", pp. 728. Price: 21s.

This is a new translation of Freud's book on dreams. It includes changes and additions made by the author with explanatory notes and an historical introduction.



## The Medical Journal of Australia

SATURDAY, OCTOBER 29, 1955.

*All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.*

*References to articles and books should be carefully checked. In a reference the following information should be given: surname of author, initials of author, year, full title of article, name of journal, volume, number of first page of the article. The abbreviations used for the titles of journals are those adopted by the Quarterly Cumulative Index Medicus. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.*

*Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.*

### THE PENSIONER MEDICAL SERVICE.

THE average member of the community will probably say that the Pensioner Medical Service is supplying a national need. People who give it serious thought will look on it as a stroke of genius, for it has brought some kind of benefit to everyone connected with it. As is right and proper, the pensioner has received most benefit. Most pensioners have more than a difficult time trying to make both ends meet; how some of them manage it, if they really do, is beyond comprehension. It is hard to imagine what it has meant to pensioners that they have lost their apprehensions about the expense in the matter of sickness. They now receive individual attention in their own homes or in the surgery from the doctor of their choice, whereas they had formerly to wait interminably for a much less personal type of attention in the inhospitable waiting rooms of public hospital out-patient departments. Benefits accrue also to doctors, pharmacists and hospitals. Doctors who treat pensioners, instead of doing so as honorary medical officers of hospitals or for a reduced fee or for no fee in their private practices, treat them in the same way as they treat their ordinary private patients for a fee agreed upon by the profession and the Government. The members of the profession are also well aware that the pensioners consult them because they want to and not because they (the doctors) are members of a hospital staff or other impersonal organization. In other words they

know that between themselves and their pensioners there is the making of an eminently satisfactory doctor-patient relationship. Pharmacists reap the advantage of being able to dispense for a reasonable fee medicines which in the absence of a pensioner medical service would be obtained at a hospital out-patient department. Hospitals have been relieved of much of the overcrowding in out-patient departments, and their beds accommodate fewer old people who have deteriorated to in-patient status because they could not afford preventive medical care. Mention should also be made of the fact that many family budgets have been freed from the burden of payment for the medical care of the old and infirm. Finally, although it may appear a little ungracious to remind them of the fact, politicians receive the kudos of having provided a most necessary service to the public.

The Pensioner Medical Service came into operation in February, 1951, and its conditions were extended in July of that year to cover the provision of special pharmaceutical benefits. We all know how the service is run—that the pensioner is issued with an entitlement card, that this card is the authority for the doctor to provide medical attention under the provisions of the service, that the card must be presented to the doctor whenever medical treatment is required, that the doctor initials and dates the card at the time of each consultation, and that the patient (or other responsible person) at the same time signs a voucher, which provides the basis of the doctor's claim for payment for his services. All this is quite clear and simple and it is only to be expected that pensioners have availed themselves of the benefits provided for them. An opportunity to estimate the success of the service has been provided by "Information Bulletin, Number 5", issued recently by the Minister for Health, Sir Earle Page. This document shows that since the inception of the service there has been a steady increase in the number of pensioners and dependants who have received benefits. We read that "the main reason for this increase is the widening of the pension field by the progressive liberalization of the means test". It may be mentioned in passing that it is the liberalization of the means test in the Pensioner Medical Service which has given and is giving great concern to the whole medical profession and particularly to the Federal Council of the British Medical Association in Australia, which is its mouthpiece in consultations with the Government. At the meeting of the Federal Council, held in August last and reported in this journal in the issue of September 24, 1955, it was resolved that certain fees would be acceptable in respect of the Pensioner Medical Service for a period of two years as from November 1, 1955, provided no new categories of pensioners were added, that is, provided no further liberalization of the means test took place. But this is by the way. Our "Information Bulletin" shows that the number of persons enrolled, that is, pensioners and dependants, has risen from 432,196 at June 30, 1951, to 640,229 at June 30, 1955. The latter figure represents 97.3% of persons eligible for enrolment in the service. In the first quarter of its operations, the service provided 228,746 individual medical services, the average number of services per year for each doctor being 230. In the quarter ended June 30, 1955, the total number of services was 1,144,646. This meant that

each person was receiving on an average 7.2 services a year, and the average annual number of services for each doctor was 1000. Since the inception of the service no less than 14,773,525 services were given up to the end of June, 1955. The number of doctors participating in the service at June 30, 1955, was 4567, and the average annual payment to each of them including mileage was £552. The total cost of medical services for 1954-1955 was £2,481,381; travelling cost amounted to £34,696, the grand total for the year being £2,516,077. It is interesting to note that the number of services given in pensioners' homes is almost the same as the number given in the surgery. During the year ended June 30, 1955, the number of the former was 2,346,181, while the total of the latter was 2,375,300. In this year, too, the number of prescriptions issued in connexion with the service was 4,418,661, and their average value was 5s. 11d.

The foregoing short review of the advantages and achievements of the Pensioner Medical Service shows that it is a service worthy of respect which should be cherished and maintained at the highest possible ethical level. Unfortunately its set-up, the type of persons for whose benefit it is drafted, and the ailments from which they are likely to suffer are such that exploitation by the unscrupulous is easy and even exposes them to temptation. Medicine and pharmacy, like every other avocation, have their scallywags and go-getters, and they find the Pensioner Medical Service ready at hand. Everyone knows that some medical practitioners are abusing the Pensioner Medical Service, and most of us realize that the good name of the profession is being besmirched. The members of the profession know that the wrong-doers are few in number; but the public, as can be easily understood, thinks that the many are like the few and all doctors are given a bad name. The Federal Council at its last meeting was very concerned with abuses that had been investigated. If it was possible to publish details of some of the cases which come before Committees of Inquiry, members of the profession, to say nothing of the general public, would be appalled. As was pointed out at the Federal Council meeting there is not enough publicity in this matter. Publicity is needed after a decision has been made and a penalty inflicted. This often takes far too long. From all States come reports that recommendations are made to the Minister through the Director-General of Health and long periods of time elapse—even months—before any decision is reached. Sometimes it seems that the Minister is afraid to consent to a punishment. If a punishment is inflicted it is of no use whatever unless it can be publicized so that it will act as a deterrent to other possible offenders. If a fine is inflicted on a wrong-doer and the fact is not stated in a Government Gazette, the fact is not known and the fine becomes in effect a licence for future misdemeanours. The Federal Council resolved to recommend to the Government that more publicity than at present should be given to offences committed by medical practitioners under the *National Health Act* and that the names of those found guilty of such offence and the nature of the offences should be published. Many persons hold, and rightly, that penalties should be severe if they are to be real deterrents. Strong action is needed to save a service which is so valuable that it is essential to our national well-being.

## Current Comment.

### THE NATURAL HISTORY OF STREPTOCOCCAL INFECTIONS.

STREPTOCOCCI of various types play a very important role in the production of disease in man, and although our knowledge of streptococcal infections is not complete, it is gradually becoming apparent that careful study of the natural history of the disease is leading to better methods of control. During the past five years the staff of the Streptococcal Disease Laboratory in Wyoming, United States of America, has made extensive investigations on streptococcal diseases, and the director, C. H. Rammelkamp<sup>1</sup>, has summarized the present state of our knowledge of the streptococci in relation to certain diseases. Most infections in man by streptococci are caused by organisms belonging to Group A. These organisms commonly invade the tissues of the upper part of the respiratory tract producing a disease which is generally sufficiently distinctive to be easily recognized. Characteristically the disease begins with the sudden onset of a sore throat followed by fever, headache and malaise. The sore throat is severe and the oro-pharynx characteristically diffusely red. The majority of persons infected with Group A streptococci develop these symptoms, but about 20% develop sore throat without marked constitutional symptoms, and a few develop no symptoms. What proportion belong to the last group is not known, but they make effective control measures exceedingly difficult. Various types of complications may occur, but of primary concern are acute glomerulo-nephritis and rheumatic fever. Acute nephritis is a relatively uncommon complication of most Group A streptococcal infections. Certain strains are very much more nephritogenic than others. Types 12, 4 and a new type and perhaps 25 account for the cases of nephritis in the United States of America. Type 12 streptococcal epidemics are the commonest to be associated with acute nephritis, varying from 5% to 13% of those infected. Once type 12 or type 4 streptococcal infections are introduced into a large city, the prevalence of nephritis may be maintained at high levels for several years. In Honolulu an epidemic of nephritis began in 1950 and has continued at high levels since.

The patient who subsequently develops acute nephritis from a type 12 infection is likely to show moderate hæmaturia during the febrile stage of the streptococcal infection and to excrete more red cells in the urine. Once nephritis occurs, the physician should examine the urine of all contacts for red corpuscles, for many cases of inapparent nephritis may be discovered. In the majority of cases patients with acute nephritis due to Group A streptococci recover within several weeks or months, and recurrences are rare, so that prophylaxis is not required in the patient who has recovered. Acute rheumatism may develop following infection with any type of Group A streptococci. The attack rate is usually about 3%, but another 3% develop a mild illness which could not be diagnosed as rheumatic fever. It is from this group that many of the persons who develop valvular diseases in later life come. So much has been written lately about the association of streptococcal infections and reinfections and rheumatic fever that it is not necessary to add anything more here.

The survival of Group A streptococci as human pathogens appears to be dependent on man himself, and most commonly the organism is found in the upper respiratory tract. The carrier state has not been considered injurious to the patient who has recovered from an acute streptococcal infection, but rheumatic fever does not occur unless the organism continues to reside in the oro-pharynx. Elimination of streptococci by penicillin even after the patient has recovered from his acute attack is wise.

During the first three weeks following infection there is a rapid decrease in the number of streptococci in the

<sup>1</sup> *Bull. New York Acad. Med.*, February, 1955.

respiratory tract, and alteration takes place in many of the remaining streptococci by failure to develop M protein, with the result that infectivity is greatly reduced. Individuals who harbour streptococci in the nasal passages are at least three times as dangerous as those who carry them only in the oropharynx. Considerable emphasis has been placed on the role of environmental reservoirs in the spread of disease and maintenance of the organism. Dust, blankets and clothing have been found to harbour Group A streptococci in large numbers, but direct experiments at the laboratory have shown that the streptococci in such environments are not important in the spread of respiratory disease; indeed there is doubt whether they ever produce respiratory infection.

### THE TREATMENT OF PULMONARY TUBERCULOSIS.

In the Lettsomian Lectures for 1955 Dr. J. G. Scadding, who visited this country last year, has given a statement of his current policy in regard to the management of pulmonary tuberculosis which he hopes will have practical value before "it becomes no more than a historical curiosity". Value indeed it has, for it is a wise, well-balanced and critical appraisal of a complex and controversial subject which may be ultimately resolved more by the eradication of tuberculosis than by due evaluation of the merits of the various therapeutic possibilities. A vast and increasing literature deals with the problem, but a summary of Scadding's views will serve to indicate current trends. By way of introduction, he points out that primary infection now tends to occur more in young adults than in children; in the former group it is the pulmonary rather than the glandular component which is predominant, with an increased risk of the development of progressive pulmonary tuberculosis. As the prognosis of this type of disease may conceivably be different from that which has commenced long after a primary childhood infection, it follows that comparisons of series treated yesterday, today and tomorrow, as it were, may not be valid in assessing the relative efficacy of the treatments employed. This point, although there is no proof of its truth, is very far from being an academic consideration.

Scadding reviews the various pathological factors which may influence the plan of treatment adopted: the development of the more or less solitary and localized caseous focus the behaviour of which cannot be predicted, the prevention of cavity closure by surrounding fibrosis or partial occlusion of the draining bronchus, and the significance of tuberculous bronchitis, particularly in relation to the development of bronchial stenosis, bronchial "cold abscess" and bronchiectasis. Broadly speaking, as will appear, these three processes are related respectively to three therapeutic problems: whether to treat actively or to observe, the role of collapse therapy and the role of resection. While an appreciation of the morbid anatomical changes is vital to the proper planning of treatment, Scadding lays due stress on the importance of social and economic factors, on the patient's previous history of tuberculosis and on his family history, on observation of the patient over a period of time and on his response to initial treatment.

Scadding introduces his discussion of chemotherapy by reviewing the problem of the development of bacterial resistance, an approach which is justified by its importance not only to the individual but to the community as a whole. It is now accepted that the more extensive the disease, the greater the constitutional disturbance; and the larger the cavities, the more rapidly will resistant strains emerge and the more resistant will they be. As the mutation required to produce resistance is different for all three of the commonly used drugs, the rate of emergence of resistant strains is considerably reduced by using any two in combination, provided the bacilli are sensitive to both drugs at the commencement of treatment. Adequate dosage is of first importance, but the necessary

dose of an individual drug varies according to the combination employed. Thus PAS is effective with isoniazid (200 milligrammes per day) in doses of 10 grammes daily, but a dose of 20 grammes daily is desirable, although not always attainable, when given daily with streptomycin (one gramme). Daily administered streptomycin with isoniazid, in the doses mentioned, is effective in reducing the incidence of organisms resistant to either drug, but isoniazid resistance tends to develop if the streptomycin is given only two or three times per week. Streptomycin given intermittently is possibly better combined with PAS, although this regime is probably inferior in this respect to the administration of both drugs daily. It is, of course, clear that once a strain of organisms has appeared which is resistant to one of a pair of drugs, then it is only a matter of time before resistant strains to both drugs are to be found. In considering the problem of drug resistance in general, it is important to remember that a laboratory report of resistance may mean that only a small proportion of the bacteria present in the lesion are actually resistant, so that the drug may continue to have some therapeutic effect, and that isoniazid-resistant bacilli may have lost much of their pathogenicity.

From the point of view of clinical effectiveness, streptomycin combined with isoniazid is perhaps slightly better than either of the other two possible "pairings". As these two drugs are individually the most potent antibacterial agents, Scadding feels that there is a case for keeping one of them in reserve; in general he tends to begin treatment with streptomycin and PAS (one gramme daily and 20 grammes daily, respectively), particularly in cases with acute, extensive and cavitated disease, in which bacterial resistance is most likely to occur. It is fair to state that many clinicians would not accept this view, preferring to give streptomycin and isoniazid, the latter perhaps in much larger doses than used by Scadding, of the order of eight milligrammes per kilogram of body weight per day. Alternatively, there is a good case for using all three drugs in the initial phase of treatment. Isoniazid and PAS are a convenient combination, for both can be given orally; they are therefore particularly useful in the treatment of older patients and out-patients. It is apparent that initial treatment with a pair of drugs is based upon the assumption that the infecting bacilli are sensitive to all three drugs. If the patient has had previous chemotherapy this assumption is not justified; and in fact if he has been treated with one drug alone in the past, it is justifiable to assume the presence of resistance to it. Similar considerations must be borne in mind where it seems possible that the source of infection is a close contact who has been treated for tuberculosis with antibacterial drugs. In these circumstances Scadding advises waiting for the results of sensitivity tests before starting treatment—ideally one would like to know the results of these tests in all cases—and he supports his argument with the statement that few patients kept at rest will deteriorate in the interim. Presumably there are exceptions to this cautious counsel. Certainly it is not a policy which is easy to carry out when other patients in the ward are all receiving active treatment, nor is it economically altogether satisfactory; again there seems to be a good case for giving all three drugs until the sensitivity tests are completed.

While its greatest value lies in its ability to promote resolution of acute pneumonic lesions without other treatment, chemotherapy has a part to play in the management of all forms of active tuberculosis. On the one hand, there is the symptom-free patient with presumably tuberculous lesions found on routine radiography, but presenting no other evidence of activity. Resolution of the shadows after a course of PAS and isoniazid (which can be given to out-patients and which does not influence any other disease but tuberculosis) indicates activity and the need for thorough treatment; absence of resolution suggests that the disease, if tuberculous, is inactive. On the other hand, there are the patients with chronic extensive disease for which no more active therapy is appropriate to whom chemotherapy offers a chance of considerable improvement. Scadding wisely emphasizes to these patients the great

<sup>1</sup> *Lancet*, July 9, 16 and 23, 1955.



importance of taking the most careful precautions against spreading infection, for the bacilli are likely to become resistant. Referring to the use of antibacterial drugs as the sole method of treatment of tuberculosis, Scadding points out that the decision to use no other measures can be made only after assessment of response, and that it is justifiable when there is persistent shadowing indicative of encapsulated caseous foci and/or fibrosis but no evidence of persistent cavitation. On the other hand, he makes a plea for avoiding unnecessary delay in adopting whatever measures may be deemed advisable to deal with persistent cavitation or in employing "medical" collapse treatment in an attempt to prevent the development of irreversible changes in some cases of acute and extensive disease.

Few methods of treatment have suffered such a rapid decline in popularity as artificial pneumothorax, and Scadding observes that in his view those centres which have entirely abandoned it are mistaken. He uses it when the disease affects the upper lobe or apical segment of the lower lobe and is predominantly of pneumonic type, with or without cavitation, but in cases in which he judges there is considerable risk of residual and persistent cavitation. Unfortunately it is inevitable that any statement of this nature will convey a different meaning to different observers, and it can only be said that in Scadding's hands the results are very satisfactory. He emphasizes that the complications of artificial pneumothorax are much less to be feared than formerly because of the advent of chemotherapy. Pneumoperitoneum, in Scadding's view, should not be employed without phrenic paralysis, and therefore should not be used when there is a likelihood of future surgical intervention, more particularly when this may involve upper lobectomy. Use of the method is suggested in the presence of acute pneumonic disease of the lower lobes or of generalized but predominantly unilateral disease; in these instances the selective relaxation upon the lower (and especially the posterior) parts of the lungs may facilitate healing without the development of cavitation.

In regard to surgical collapse measures, Scadding's enthusiasm for the operation of plombage is surprising, although perhaps less so when it is appreciated that he has the collaboration of W. P. Cleland, the surgeon responsible for the development of the best available technique for its performance. Certainly it is less deforming than thoracoplasty, and it can be performed in one stage; these reasons lead to its preference where the cavity to be dealt with lies within the upper one-third of the lung. Only two of 44 plombes have required conversion to thoracoplasty because of post-operative infection of the plombe space. Resection may be considered when the disease is strictly localized, notably in lesions of the bronchial cold abscess or residual caseous focus types, more particularly when there is evidence of cavitation awkwardly placed for collapse measures. When strictly localized to one lobe and unlikely to heal with prolonged conservative measures, the disease may be considered best treated by lobectomy, usually with a modified thoracoplasty when the upper lobe is removed. If similar criteria are used, pneumonectomy may rarely be indicated. When localized cavitation is all that remains of previously extensive disease, resection may "reasonably be undertaken", although for apical cavities Scadding would prefer to adopt thoracoplasty or plombage. The presence of bronchial disease, usually in the form of bronchial stenosis, indicates the need for resection rather than for collapse measures.

The variety of combinations and permutations of an increasing number of treatments require that the physician shall keep an open mind and treat each patient individually rather than according to any preconceived plan; the decisions to be made after an initial period of bed rest and chemotherapy are perhaps the most crucial in this regard. Despite the invaluable information gleaned from such projects as those conducted by the Medical Research Council, Scadding points out that for various reasons similar precise data concerning the effectiveness of different regimes in different types of pulmonary tuberculosis are never likely to be presented. Dr. Scadding's

reasoned approach to these problems may be regarded as conservative in many centres today, but he has clearly aimed at the rational compromise which is the usual outcome of violent oscillations of the therapeutic pendulum in the history of medicine.

## AUTOMOBILE INJURIES.

THE typical injuries that occur in automobile collisions at the higher speeds are those of a body decelerating very rapidly through striking a hard and irregular structure. Nevertheless, in common with the minor injuries which occur because of the particular qualities of automobiles, they comprise, mainly, a special group with special characteristics. One, which used to be very common when engines had to be started by cranking, was the "chauffeur's fracture"—a sort of reversed, unimpacted Colles's fracture. Also uncommon is cut throat caused by the head's being forced through the windscreen, and the throat's being dragged down onto the broken glass by the weight of the body; modern safety glass does not break in that way. "Steering-wheel chest", the anterior type of stoving in, usually with paradoxical respiration, has always been with us, as have fracture or upward dislocation of the patellæ due to impact with the edge of the dashboard, and depressed fractures of the facial bones, commonly called "pilots' fracture", due to the head's being jerked forward onto the dashboard. Broken necks and backs, the result of the victim's being thrown across the back of a seat and being crushed by it when the car rolls over, are less common now that metal bodies are strong enough not to collapse, but can occur in convertibles, and often occur in jeeps. Various fractures of arms and skull, combined with extensive and deep abrasions, are caused when a door opens and allows a passenger to be thrown onto and skidded along the road; children are the more frequent victims of this type. These are all more or less routine; one, a newer type, is decapitation of all those in the front seat when the car runs under the high projecting tray of a large truck or semi-trailer. "Small-car fracture", which occurs in drivers, gets its name because in small cars the open window is of a most convenient height for the driver to rest his right arm and leave his elbow projecting far out; a passing vehicle can break the ulna just below the elbow by direct force, and the humerus just above by levering it against the door frame, often shattering the joint as well. Running-over accidents have lately been paid some attention; rupture of a bronchus without fracture of ribs, in a child, has been reported, and various types of stove-in chest are often mentioned. J. B. Prendiville and Emlyn Lewis<sup>1</sup> have recently described the "pneumatic-type torsion avulsion injury" and its treatment. This occurs when a limb is completely run over, especially by a heavy, slowly moving vehicle with wide tires; they mention, but do not give it the emphasis it needs, the contributory effect when the wheels are braked at the time of running over. The mechanism of the injury is that the road and the tire grip the limb, the skin is drawn and stretched and the contents of the skin are forced ahead, producing disruption, first at the level of the deep fascia and then at the skin level, allowing muscles *et cetera* to be forced out and further damaged. The end result (because major vessels and nerves are infrequently involved) is gross tissue loss in a viable limb. Of course, extensive tight suturing makes it almost inevitable that Volkmann's ischæmia will develop and cause limb loss. Wide excision and early reconstruction are needed. Surprisingly useful limbs, in spite of the avulsion of whole groups of muscles, are reported. As stated above, the authors have not sufficiently emphasized the destructive effect of a limb's being run over by a wheel almost or completely locked by braking—this does much more damage than the quick pressure of a freely rolling wheel, which may sometimes cause no more than severe bruising. A Sydney traffic policeman was once reported to have said:

<sup>1</sup> Brit. J. Surg., May, 1955.

"If they must run over people, why must they do it with their brakes hard on?" Applying the brakes when an accident threatens is an automatic reaction, of course, and superhuman calmness and judgement would be necessary to decide that actual running-over was inevitable and to release the brake pedal at the correct moment and then apply it to prevent the rear wheels' also running over the victim. Such judgement would have perhaps altered the result of an unpleasant accident in Sydney a few years ago, when a truck driver finally managed to stop his vehicle as the wheel mounted the body of the victim—yet, on the other hand, if he could have stopped a foot shorter, little damage would have been done. Probably this discussion has become too academic. At any rate, just as "chauffeur's fracture" could be avoided by correct placing of the thumb on the cranking handle, so "small-car fractures" can be avoided by keeping the elbow within the vehicle, and some of the newer types of accidents could be avoided by better automobile design, just as some of the older types have already disappeared because of improved design.

#### CELLULAR PATHOLOGY.

A DISTINGUISHED PHYSICIAN recently asked whether possibly we were giving too much time to inventing new drugs to treat disease instead of investigating the cause of disease and the means of preventing it. That was a fair question, but the difficulty is that we have reached a point at which the easily prevented diseases have been dealt with, but we have not sufficient knowledge of basic processes, both physiological and pathological, to enable accurate preventive methods (or even specific methods of treatment) to be framed for dealing with the more complicated conditions. The simpler ways of investigating the working of the body in health and disease have been exhausted, and the methods of making detailed micro-investigations are long, tedious, highly skilled and vastly expensive—many of them are only yet in process of being invented. Still, every here and there are workers busily engaged in ferreting out the minutest secrets of the body. G. R. Cameron,<sup>1</sup> in the John Mallet Purser Lecture delivered at Trinity College, Dublin, last May, described new fields in cellular pathology as revealed by work done at the University College Hospital Medical School, London.

Cameron described how tissues are cut up with a specially designed mincer and then homogenized. By means of differential centrifugalization at 700G., 9000G. and 20,000G. to 30,000G., nuclei, mitochondria and microsomes are separated and can be studied, and used as tools for the investigation of metabolic and enzyme activity. Work on these cell "organelles" is now proceeding, but there remains a vast field yet to be explored. It is known, for instance, that the mitochondria (of which there are some 2500 in a single liver cell) are the centres for liberation of energy from food; they handle the metabolism of fats, proteins and carbohydrates through a great variety of oxidations and reductions catalyzed by a series of enzymes and co-enzymes. Experiments with a poisonous substance such as carbon tetrachloride have shown that it is attracted especially by the phospholipids of the mitochondria; its presence interferes with the early stages of fat breakdown and also with later stages of the cycle. The consequence is an accumulation of fats and their immediate products. It is known that carbon tetrachloride poisoning causes fatty changes and then cell death in the regions of the centrolobular cells of the liver and in the convoluted tubules of the kidney. When these tissues are broken up, the granules and vacuoles can be tested; they have been proved to be either mitochondrial derivatives or distorted mitochondria. The whole process of the development of cloudy swelling has been followed by taking serial biopsies from rats suffering from carbon tetrachloride poisoning.

<sup>1</sup> *Irish J. M. Sc.*, August, 1955.

Working along similar lines, Opie, in 1949, showed that many cells are not in osmotic equilibrium with their environment—certain liver and kidney cells are hyper-osmotic. Such cells must have means of preventing excess fluid from entering, or of getting rid of it; these activities are probably located at the surface membranes of the cells and their organelles. A shortage of oxygen is the factor which causes a breakdown in this mechanism and the development of hydropic degeneration. Moreover, by injecting serum albumin tagged with  $I^{131}$ , and later examining the separated organelles of renal cells, the destination of the albumin can be determined, in health and in conditions such as nephrosis. Spector has found that four to ten times as much albumin is taken up by tubule cells, mainly in the mitochondria and microsomes, when nephrosis is present; at the same time, the cells show a type of cloudy swelling, indicating that this condition is due to increased protein loading following accelerated cell activity.

Cameron also described how these methods had proved that the mechanism by which thioacetamide produced inhibition of the oxidation of pyruvate and other substances was by so altering the permeability of cells that cell calcium increases fiftyfold, while magnesium and potassium are lost; the calcium accumulates at the surfaces of the mitochondria. Furthermore, although this altered permeability is demonstrably not due to the liberation of histamine, it has been found that antihistamines reduce or reverse the effect.

Investigation of the effects of copper deficiency in causing demyelination of the spinal cord led, as a sideline, to the discovery of other mitochondrial activities, physical and chemical. Although, as Cameron pointed out, these are but a few of the investigations that are taking place, and are as yet incomplete, nevertheless the bringing together of the information so gained, and still to be gained, must inevitably lead to our understanding of the fundamentals of disease processes some day, and then we shall be able to prevent diseases, as well as treat them, with an accuracy not possible today.

#### MEPACRINE AND TAENIA SAGINATA.

EXTRACT of male fern is neither pleasant to take nor extremely efficient in expelling tapeworms, so that the technique described by D. R. Seaton<sup>1</sup> for using mepacrine in its stead should be welcome. He states that the patient should be kept at rest and given liquids only for two days. On each day a saline aperient is given, and on the second day an enema. On the second evening "Sodium Amytal", three grains, is given, and a Ryle's tube is passed. By the next morning the end of the tube should have passed well beyond the pylorus (this could be checked by X-ray examination). On this third morning mepacrine, one gramme dissolved in 100 millilitres of warm water, is squirted gently down the tube with a syringe; fifteen to thirty minutes later, 1.5 to 2.0 ounces of magnesium sulphate in 100 millilitres of warm water are injected down the tube, and the tube is then withdrawn and the patient is given a hot drink.

Seaton points out that the preliminary starvation is essential, and that the prompt purging is needed to sweep the worm from the intestine before it has had time to recover from the effects of the mepacrine, which does not kill it, but causes it to detach itself and become tightly contracted. The use of the Ryle's tube ensures that the medicaments will be retained, and that they will be delivered in full concentration in the neighbourhood of the attachment of the scolex. Of a series of 15 patients, Seaton reports that 12 passed a complete worm at the first treatment, two others needed a second treatment, and the fifteenth could not get the tube past her pylorus, and vomited the mepacrine. These figures certainly suggest that this method of treatment is effective.

<sup>1</sup> *Lancet*, September 24, 1955.

## Abstracts from Medical Literature.

### DERMATOLOGY.

#### Local Treatment of Dermatitis with Hydrocortisone Acetate.

H. M. ROBINSON, JUNIOR, AND R. C. V. ROBINSON (*J.A.M.A.*, July 31, 1954) state that the value of topical application of hydrocortisone acetate in the symptomatic treatment of various dermatoses is confirmed. Their results in the treatment of atopic dermatitis and ano-genital pruritus were very good, but relapses occurred when treatment was discontinued. Strengths of less than 1% of hydrocortisone acetate were mostly ineffective.

#### Treatment of Vitiligo with Psoralen Derivatives.

W. M. GEORGE AND J. W. BURKE (*Arch. Dermat. & Syph.*, January, 1955) state that psoralen derivatives are crystalline principles extracted from *Ammi majus* Linn. fruits which are found abundantly in the Nile Delta. Since the thirteenth century Egyptians have used a powder prepared from the fruit of this plant for treatment of vitiligo. The powder was recently investigated by Fahmy and Shady, and they successfully isolated three crystalline substances which they named ammoidin, majudin and ammidin. El Mofty used the three compounds separately and in various combinations. The drugs are administered orally as well as locally as an alcoholic paint applied to involved areas with constant exposure to ultra-violet light or sunshine. If actinodermatitis occurs, treatment must be delayed. Eleven Negro patients with vitiligo were treated with psoralen derivatives used locally as ointment alone or in conjunction with orally administered tablets. Fairly good results were obtained with either method.

#### Local Action of Heparin on Xanthomata.

T. CORNBLEET (*Arch. Dermat. & Syph.*, February, 1955) states that xanthomata were given a series of injections with heparin sodium solution. The drug was deposited within and under the lesions. Usually one selected site was worked on at a time, and an amount of no more than one millilitre or 5000 units was used at each treatment. More than this could possibly induce a bleeding state. A fine needle is used, and little bleeding occurs. Treatments are given once or twice a week. The first two or three injections have little gross effect on the lesions, but succeeding ones become progressively more capable of reducing the size of the lesions. Prothrombin times are determined on the day of the first injection and again six to twelve hours after treatment. If the results are within fairly safe limits, then we may assume it permissible to continue further injections without checking the prothrombin time. All subjects were advised to watch for bleeding tendencies and to avoid situations exposing them to injury. In eight cases of xanthomata, heparin

injected into the lesions caused them to flatten and disappear.

#### Treatment of Onychomycosis due to *Trichophyton Rubrum*.

B. M. KESTEN, R. BENHAM AND M. SILVA (*Arch. Dermat. & Syph.*, January, 1955) state that in a group of patients suffering from onychomycosis due to *Trichophyton rubrum* the infection of the nails varied from a mild thickening of the distal edge to complete involvement of the nail plate. All patients had associated skin lesions, and *Trichophyton rubrum* was recovered from the skin of one or more affected areas. The patients were instructed to cover the infected nails with cotton pads soaked with a 65% aqueous solution of lithium bromide for at least one-half hour every night. Afterwards the nails were sprayed with a solution containing approximately 16% of dextrose and 4% of "Asterol" dihydrochloride. When dry the nails were painted with nail lacquer containing about 10% of lithium bromide and 6% of "Asterol". On the following night the lacquer was removed with acetone, and the procedure was repeated. The nails were rimmed with petrolatum to help prevent chemical paronychia. However, when this developed, only the lithium bromide-"Asterol" nail lacquer preparation was applied to the nails for a few days. At intervals much of the diseased nail was removed with clippers and a dental burr. Further cultures were prepared from affected nails when improvement was noticed. If there was no growth on Sabaroud's medium, additional cultures were made on media containing antibiotics and cycloheximide. With two negative culture results and the regrowth of a normal nail the infection was considered cured. By these methods two patients were cured and 19 obtained improvement.

#### Treatment of Pyogenic Dermatoses with Tetracycline Hydrochloride.

L. C. GOLDBERG (*Arch. Dermat.*, May, 1955) presents a report based on clinical findings resulting from the sole or supportive treatment of 145 patients with selected dermatoses by means of tetracycline ("Tetracyclin"). All the patients had some type of pyogenic skin disease; 14 had *impetigo contagiosa*, 40 the pustular phase of *acne vulgaris*, rosacea and *acne necrotica*, eight *herpes zoster*, two oral aphthous ulcers, four chaneroid, 34 impetiginized dermatoses, 22 local and generalized folliculitis, three secondary burns, 14 infectious eczematoid dermatitis and four hidradenitis. The untoward reactions were few; amongst these were pruritus, gastric distress, urticaria (in two cases), and severe *erythema multiforme* (in one case). Blood and urine studies were carried out on patients selected at random, and no abnormalities were noted. Tetracycline hydrochloride in doses of 250 to 1500 milligrammes daily controlled infections of the skin easily and promptly. It cured chaneroid and prevented infections in secondary burns. It controlled infections such as *impetigo contagiosa*, the pustular stage of *acne vulgaris*, rosacea and *acne necrotica*, folliculitis, impetiginized dermatoses, infectious eczematoid dermatitis and hidradenitis. It was of

no value for aphthous ulcers of the mouth and did not affect the course of *herpes zoster*.

#### Ecthyma Contagiosum (Orf).

C. E. WHEELER, E. P. CAWLEY AND J. H. JOHNSON (*Arch. Dermat.*, April, 1955) state that *ecthyma contagiosum*, also known as orf and ovine pustular dermatitis, is a virus disease of sheep and goats which is occasionally transmitted to man. Cases have been reported from many parts of the world. The lesions of *ecthyma contagiosum* in man usually appear on exposed surfaces, especially the face and hands, as a result of direct inoculation from infected animals. The lesions, which vary in number from one to several, appear in four days to a week after inoculation and go through macular, papular, vesicular and crusted stages. The entire process occupies approximately four weeks in an uncomplicated case. Constitutional symptoms are usually absent. There may be low grade lymphadenitis, and local pyogenic complications may occur. The disease is self-limited, and treatment is directed entirely towards prevention or cure of secondary infection. It has to be differentiated from milker's nodes, pyogenic granuloma, accidental vaccinia and pyoderma of various kinds.

#### Silicon Granuloma of Skin.

P. M. CROSSLAND (*Arch. Dermat.*, April, 1955) states that the characteristic features of silicon granuloma of the skin are as follows: a history of trauma involving some siliceous material, a long latent interval and appearance of papular or nodular lesions at the exact site of injuries, often in scars. Microscopically all lesions show a typical sarcoid reaction, with doubly refractile crystalline material demonstrable under polarized light. Conclusive proof of the siliceous nature of anisotropic crystals seen in sections can be established by means of microdissection and X-ray absorption spectrography. In diagnosis, sarcoidosis and tuberculosis must be ruled out by concomitant systemic findings. However, silicon granuloma may be present in association with either of these diseases. It is suggested that silicon may play an active role in the development of granuloma from traumatic contact with broken fluorescent bulbs. A case is reported of traumatic silicon granuloma of the skin with papular lesions which subsided without treatment.

#### Cutaneous Manifestations of Myelogenous Leuchemia.

M. J. COSTELLO, O. CANIZARES, M. MONTAGUE AND C. M. BUNCKE (*Arch. Dermat.*, May, 1955) report four cases of myelogenous leuchemia, each presenting different cutaneous reactions; one consisted of ulcerating tumours, a second was represented by generalized nodular plaque-like lesions associated with pulmonary tuberculosis, a third manifested itself by petechiae, haemorrhagic blotches and haemorrhagic bullae, and a fourth exhibited a combination of the others. The authors state that difficulty in early diagnosis is the rule. The therapeutic test with X rays is offered



as an aid in differentiating the radio-sensitive specific infiltrative cutaneous diseases which simulate them, especially certain types of *lupus erythematosus*. Cortisone was of value in controlling symptoms of the disease.

## UROLOGY.

### Urinary Surface Tension and Colloids in Urolithiasis.

R. A. RAVICH AND A. RAVICH (*J. Urol.*, December, 1954) state that the work of Butt, Hauser and Seifter, published in 1953, has focused attention on the role of surface-active colloids in inhibiting the precipitation and agglomeration of inorganic matter in the urine and preventing the formation of renal calculi. Studies concerning this intriguing new approach to the problem of urolithiasis are limited by the complexities of available methods for determining the concentration of colloids and urinary surface tension. The urotensiometer recently designed by Revici provides a simple, inexpensive instrument capable of giving accurate surface tension values in a few seconds. Readings are made directly in degrees per centimetre. Studies have shown that surface tension values are higher in patients with urolithiasis and urostasis than in patients with other urological or non-urological diseases. When the surface tension is low, it means that the concentration of colloids and of unassociated surface active ions or molecules is high; the reverse state of affairs is also true. The findings suggest that the Revici urotensiometer can be useful in guiding therapeutic measures aimed at maintaining a high level of excretion of surface active substances in the urine of patients in whom it is necessary to reduce the tendency to stone formation.

### Vesical Neck Resection in Neurogenic Bladders.

A. E. COMARR (*J. Urol.*, November, 1954) makes a statistical analysis of 151 patients in whom it was judged that endoscopic resection of the vesical neck would probably be useful in restoring imbalance between the detrusor and the sphincters in neurogenic bladders. In the Veterans' Administration Service 139 of the patients reviewed here had a traumatic lesion of the spinal cord, the remaining 12 having lesions due to disease. A number of the patients had to undergo two or even three resections. In this service, the treatment of all patients with "cord bladders" consists of tidal drainage, Munro's bladder training and pudendal nerve block, as indicated, before any surgical operations are embarked upon. During the conservative period of treatment, many obstacles may arise that prolong therapy, such as peno-scrotal fistulae, vesico-ureteric reflux, pyelonephritis and urinary tract calculi, as well as non-urological complications such as decubital ulcers and spasticity. The conservative period may last from several weeks to about a year. If conservative measures fail, then operative procedures must be considered, such as endoscopic resection, pudendal nerve operations, sacral nerve operations,

anterior and/or posterior rhizotomies, subarachnoid injections with absolute alcohol and presacral neurectomy. The classification of neurogenic bladder types preferred by the author is (i) the upper motor neuron type, and (ii) the lower motor neuron type. This classification depends essentially on whether the lesion is above the *conus medullaris*, or in the *conus* (or below it). If the *conus* is undamaged (lesion above it), the reflux patterns are undisturbed. If the lesion is in the *conus* or the *cauda equina*, the reflux patterns are disturbed. The former is of the upper, the latter of the lower motor neuron type. Tidal drainage is used initially in both types. However, even in the early conservative period, pudendal block is often useful in the upper motor neuron type. If conservative measures fail, operation is called for, and in the lower motor neuron type endoscopic resection is indicated. Surgery in the upper motor neuron type consists, according to circumstances, of the following procedures, or some combination of them: endoscopic resection, pudendal neurectomy, sacral neurectomy, rhizotomy, subarachnoid alcohol block, presacral neurectomy. The author states that in a period of seven years, 151 patients out of a total of 905 with cord lesions of the bladder required endoscopic resection. Of these 151 patients 81% had a good result from the operation, 1% had fair results and 11% had poor results.

### Brucellosis of the Genito-Urinary Tract.

K. A. FORBES, E. C. LOWRY, T. E. GIBSON AND W. A. SOANES (*Urological Survey*, December, 1954) state that the diagnosis of brucellosis of the genito-urinary tract has seldom been made by the urologist. They have therefore reviewed the literature on this subject, and in addition report a personal case. They state that brucellosis, as a systemic disease of men, has been described as being more protean in its manifestations than either syphilis or tuberculosis. In 1918 Evans demonstrated the relationship between the aetiological agent in human infection, then known as the *Micrococcus melitensis*, and the organism of contagious abortion in cattle. The term *Brucella*, later proposed, was in honour of Bruce, who discovered the causal agent of Malta fever in 1887. Brucellosis is world-wide in distribution, and is regarded as one of the most common diseases transmitted from animals to man. The principal modes of transmission of *Brucella* organisms are ingestion of infected raw milk or contact with infected animals or their flesh. Brucellosis, like tuberculosis, may be localized in the genito-urinary tract at any stage of the disease. The genito-urinary manifestations may so overshadow the systemic symptoms that the true nature of the illness remains unrecognized. The pathological changes range from transient, acute genital infections to severe chronic pyelo-nephritis with calcification and permanent renal damage. A positive diagnosis is established only by cultural isolation of any of the three species. A presumptive diagnosis may be made on the basis of a positive serum agglutination reaction of significantly high titre. In treatment, "Aureomycin" and "Terra-

mycin" are the drugs of choice at the present time.

### Modification of Urinary Surface Tension by Oral Glucuronic Acid.

H. C. HARLIN AND L. WIESEL (*J. Urol.*, December, 1954) state that they obtained some insight into the problem of unpredictable urinary stone recurrence while investigating the end product of injected hyaluronidase. Subcutaneous injection of this substance produces depolymerization of hyaluronic acid. How such a change affects the surface tension of urine is perplexing, for the very large molecules of hyaluronic acid will not pass through the capillary glomerular wall, and hyaluronidase itself is rapidly inactivated by the proteins of the blood-stream. The authors therefore postulated that only highly depolymerized fractions of hyaluronic acid could enter the circulation and reach the glomerular filtrate in appreciable concentration. One of these end products is glucuronic acid, and this is available in the pure state as a synthetic chemical substance called glucuronolactone. In their studies, the authors have noted that unless there is a marked excess in the crystalloid element of the urine, stone formation does not occur when the urine has a normal surface tension value. But with a urolithiasis tendency, present or past, the patients have a raised urinary surface tension. The latter estimation can be made easily, even by the patient himself, with the new urotensiometer of Revici. The authors have been able to bring elevated surface tension values down to normal by orally administered glucuronolactose. The normal level is 66° to 69° per centimetre. The normal elevated range observed is 70° to 73° per centimetre.

### Formation of Uric Acid Calculi during Leuchæmia.

L. E. MCCREA (*J. Urol.*, January, 1955) states that uric acid calculi may develop in some patients with leuchæmia, even if not under treatment. This results from the excretion of excessive amounts of uric acid. The potent therapeutic agents of nitrogen mustard-like form, which are used in leuchæmia and also as carcinolytic agents, are triethylene melamine (TEM), triethylene phosphoramide (TEPA) and triethylene thiophosphoramide (THIO-TEPA). It is imperative that when such compounds are administered fluids should be forced to maintain uric acid solubility in the urine. Even then, the excretion of uric acid may be so excessive that calculus formation occurs, with deposition of uric acid crystals in the tubules and calculi in the calyces, with risk of uræmia and death. Therefore, in addition to adequate fluid intake and output, alkalinization of the urine is necessary. It has been established that the therapeutic use of the above compounds may cause very excessive uric acid excretion; therefore before their use an excretion urogram should be made, and during treatment the serum uric acid and blood urea nitrogen contents should be estimated daily. Any unfavourable alteration in these findings should be followed by ureteric catheterization and irrigation of the renal pelvis with an alkaline solution.

## Public Health.

### NATIONAL HEALTH AND MEDICAL RESEARCH COUNCIL: COMMITTEE ON EPIDEMIOLOGY AND INFECTIOUS DISEASE.

The Committee on Epidemiology and Infectious Disease of the National Health and Medical Research Council met at the Commonwealth Serum Laboratories, Melbourne, on July 22, 1955. The committee considered a number of matters relating to the use of Salk type vaccine as a prophylactic against poliomyelitis.

#### Purchase of Vaccine from the United States.

At its meeting in Sydney on April 26, 1955, after publication of a statistical analysis of the mass immunization test of Salk type poliomyelitis vaccine undertaken in the United States, the committee recommended that, pending production of a poliomyelitis vaccine by the Commonwealth Serum Laboratories:

The Commonwealth should endeavour to obtain from the United States, or elsewhere, 100,000 courses (of 3 x 1 c.c. each) monthly.

At the time of making it the committee qualified this recommendation by stipulating that overseas suppliers should be required to furnish protocols relating to each batch supplied, so that the Australian authority might be able with reasonable certainty to eliminate the risk of importing and using any unsafe or ineffectual vaccine.

The information available to the committee at that time led to the conviction that both the safety and efficacy of a vaccine certified by the National Institute of Health of the United States were above reasonable suspicion; and it appeared that the safety testing precautions recommended were adequate.

However, subsequent events in the United States have disclosed that this information, on the basis of which the recommendation was made, was misleading in at least one important particular. The report of the field trials raised no question of the sterility of the vaccine used, and the implied assurance that live virus had been completely eliminated was never called in question. Cases of poliomyelitis occurring in vaccinated subjects during the tests were presented as naturally occurring cases which vaccination had failed to prevent. The study of cases occurring after use of the Cutter vaccine, and later of other vaccines, in the United States mass immunization programme has since disclosed that (a) contrary to Salk's original contention, it is known that live virus may be recovered by tissue culture from batches of vaccine under preparation, well after the expected time of complete sterilization; (b) the tests originally applied to check sterility have proved equivocal and inadequate; (c) inclusion of the highly virulent Mahoney strain as the Type I component involves a very high risk of producing paralytic poliomyelitis, if vaccine which for any reason contains residual live virus is inoculated into susceptible children.

Experimentation is proceeding in the United States to overcome these defects. On the one hand an effort is being made to develop more elaborate and reliable sterility tests, and on the other hand the substitution of an avirulent Type I strain in place of the Mahoney strain is being considered.

Up to the time of this meeting (July 22, 1955) no clear policy has yet been put forward by the United States Health Authority, and the committee is of the opinion that it would be unwise to use Salk type vaccine until a final determination is made.

Members concede that Salk type vaccine in batches produced to the original formula early in the year may in due course satisfactorily pass modified sterility tests and be certified as safe, but the committee questions whether during the lapse of time since original production this will not have lost a significant proportion of its antigenic value.

Regarding vaccine prepared to any new formula and checked for sterility by any new routine, the committee cannot with confidence make any recommendation until details are available.

The delay involved in awaiting these developments in the United States, coupled with the fact that the Commonwealth's Dr. Bazeley is in fact personally associated with the experimentation and studies devoted to the development of new techniques, suggests to the committee that the Commonwealth Serum Laboratories may well be in a position to undertake the mass production of an ultimately approved Salk type vaccine as soon as any such might be expected to arrive from the United States in large quantities.

Under the circumstances the committee felt under an obligation to reconsider its earlier recommendation, and if necessary to tender new advice to the Minister. After careful deliberation the committee wishes to withdraw its previous recommendation and to advise the Minister against the immediate purchase of vaccine produced in the United States. The committee therefore recommends that:

The Director-General of Health advise the Minister that any orders placed in the United States for the purchase of Salk type vaccine should be cancelled.

#### Public Confidence.

The committee is acutely aware of the necessity of restoring and conserving public confidence in the safety and efficacy of vaccination for poliomyelitis, whether undertaken by Salk type vaccine or any other. Apart from the disquieting publicity attending the Cutter incidents, Australian public opinion must be assumed to have hardened against mass vaccination by Salk type vaccine following the published announcement that the United Kingdom and South Africa have decided not to proceed with their projected campaigns for immunization using this type of vaccine.

The committee considers that, apart from the necessity of taking all practical precautions to ensure that any vaccine issued for mass immunization will be, as far as it is humanly possible to determine, both effectual and safe, there is a real need to meet and allay public suspicion of the type of vaccine used in the initial United States mass immunization campaign. This may ultimately be achieved by recourse to one, or a combination of more than one, of the following: improved methods of processing, more efficient sterilization, more reliable safety checks, and/or the substitution of avirulent strains for those originally included in the Salk vaccine.

The possibility that vaccines of the Salk type will eventually be superseded by some type of avirulent living vaccine must be kept in mind, but in the immediate future the committee feels that the practical problem is limited to ensuring that an absolutely safe Salk type vaccine can be provided.

The committee is of opinion that it is highly desirable that the immunizing strains included in the vaccine should be avirulent. Members are hopeful that current work in the United States will permit substitution of an avirulent strain by the time the Commonwealth Serum Laboratories are in a position to undertake bulk processing.

In the meantime, however, the committee feels that Australian use of the vaccine which fell under suspicion after the Cutter episode would be unwelcome to a significant proportion of Australian parents.

#### Epidemiological Studies during Vaccination Campaigns.

Supplementary to any checks imposed by the Commonwealth Serum Laboratories, and as a further measure toward safeguarding public confidence, the committee considers that once mass vaccination of the Australian population has commenced, a carefully organized and detailed epidemiological scrutiny of all cases of poliomyelitis occurring in vaccinated subjects, or in persons closely associated with them, must be undertaken throughout the States in order to (a) resolve promptly any doubt regarding the sterility of the vaccine used; (b) verify its consistent maintenance of potency; and (c) exclude the possibility of the occurrence of coincidental poliomyelitis in vaccinated subjects being misconstrued as originating in artificial infection by the vaccine.

The committee considers that the studies involved in this routine should and could be undertaken as part of any vaccination campaign by the poliomyelitis officers of the various States. In order, however, that the study may be undertaken with a uniformly high degree of thoroughness and efficiency, it is recommended that:

Poliomyelitis officers from every State should attend a special course of instruction, in which they may be taught in detail the methods of observation and inquiry to be applied, and the procedures to be adopted for the collection of material required for the identification of virus by culture. Preparation of a curriculum for this proposed course should be deferred until Dr. Bazeley's return to Australia, so that he may be consulted at all stages, and take an active and decisive part in its preparation.

The committee met at the Commonwealth Serum Laboratories, Melbourne, at 11.30 a.m. on Wednesday, September 21, 1955, to discuss with the director and Dr. P. Bazeley the proposed production of Salk poliomyelitis vaccine.

The chairman explained for the information of coopted members that at its meeting on July 22, 1955, members had expressed concern that it had been shown possible for live virulent virus to survive formalin inactivation in some batches of vaccine produced commercially in the United States, and that this survival had not invariably been detected by the routine safety checks prescribed by the National Institutes of Health, Washington. The committee had therefore at that time deferred consideration of the proposal to manufacture the Salk type poliomyelitis vaccine at the Commonwealth Serum Laboratories until members had had an opportunity of discussing with Dr. Bazeley methods of manufacture and checking more recently introduced in the United States to eliminate this hazard. The purpose of the present meeting was to give members an opportunity of hearing from Dr. Bazeley, who had played an important part in the mass production of the vaccine in Dr. Salk's laboratory, Pittsburgh, what, if any, changes in production or checking methods were now considered necessary or desirable.

Dr. Bazeley informed the committee that subsequently to the Cutter incident the National Institutes of Health, Washington, had revised and made stricter the requirements for safety checking. He detailed the checking methods proposed to be incorporated in the Commonwealth Serum Laboratories' routine. These will be additional to, and more exacting than those prescribed as the minimum requirements of the National Institutes of Health, and promulgated on May 26, 1955.

Dr. Bazeley stated that endeavours to find a satisfactory replacement for the Mahoney strain as the Type I component of the vaccine had so far been unsuccessful. Attenuated strains supplied by Dr. Sabin had been tried, but all those tested had proved to be still pathogenic, producing paralysis following intramuscular injection. The yield of antigen from these strains had also been disappointingly low.

Dr. Bazeley was asked whether the greater apparent safety of the vaccine used in Canada was attributable, as had been suggested, to the inclusion of merthiolate in the final product as marketed. Dr. Bazeley replied that this was not so. The Canadian vaccine and the Cutter vaccine differed from other vaccines used in the United States tests to the extent that neither included any additional antiseptic in the product issued for use. He believed that the comparative safety of the Canadian product was to be explained by greater care and precision in the application of the routine safety checks.

Following discussion the committee passed the following resolutions:

1. The committee recommends that the Commonwealth Serum Laboratories proceed with the manufacture and issue of Salk type poliomyelitis vaccine believing that the intended methods of manufacture and checking will ensure a safe and effective product.
2. The committee concurs with the suggestion of the director of the Commonwealth Serum Laboratories that before the C.S.L.'s product is issued for purposes of public vaccination it should, if this can be arranged, be submitted to a final check by an independent authority not directly associated with the Commonwealth Serum Laboratories.
3. The committee expects that active research will continue in Australia and elsewhere to develop an avirulent or attenuated strain of each of the three types of poliomyelitis virus at present proposed to be used in the vaccine. Should strains be developed which can be shown by responsible authority to be potentially less virulent to humans, to possess adequate antigenicity and in all other respects to be acceptable for the production of vaccine, the opportunity should be promptly taken to substitute these for the fully virulent strains in current use.

## The College of General Practitioners.

NEW SOUTH WALES FACULTY.

RESEARCH IN GENERAL PRACTICE.

The following statement has been received from the Honorary Secretary of the New South Wales Faculty of the College of General Practitioners.

Following the informative leading article on research in general practice (THE MEDICAL JOURNAL OF AUSTRALIA, September 10, 1955), it may be of interest to record something of the progress that the New South Wales Faculty of the College of General Practitioners is making in the development of research.

### Research Register.

On joining the College each member and associate receives a circular as follows:

There was a time in the history of medicine when all research was general practitioner research, for there were none but general practitioners to undertake it. As time passed and institutional treatment became more efficient and widespread, together with the growth of specialism and laboratory facilities and technique, the role of the general practitioner in the field of research became overshadowed and sank to a low ebb.

Now the tide is running in and hospital facilities and accommodation can only cope with the severe and advanced forms of disease and accident. General practitioners are called upon to treat, in the home or surgery, the sick, sad and sorry, with complaints at a stage or of a kind seldom seen in hospital practice.

The opportunities for the general practitioner to make observations of diseased states under circumstances unique to his sphere of medical work are undeniable.

It was, therefore, to assist in opening up this sphere of medical work that the Research Committee of the College was formed and the Research Register opened.

It is planned to assist the man who wishes to work on his own, and to form study groups of men with mutual special interests, as well as organize a body of men who are willing to cooperate in a collective form of research, such as the compilation of statistical facts, the promulgation of news regarding the geographical incidence of disease, and possibly provide further clinical material for those in need.

No attempt is made to compete with existing research organizations, nor is work initiated by the College which can better be done by others. When specialized knowledge of research technique is required, advice is sought from our advisory panel of experts.

It will be seen by this brief appraisal of the methods and sphere of work we use and pursue, that all members of the College will be able to take part in some degree, and since this activity constitutes one of our major objectives and is of first importance to our prestige as a College, it is earnestly hoped that every member will fill in the subjoined form and post it forthwith.

**Advisory Panel.**—An Advisory Panel in Research has been formed and the members are: Dr. F. W. Clements, Professor Lorimer Dods, Professor E. Ford, Professor C. G. Lambie, Dr. H. O. Lancaster, Professor Bruce Mayes, Professor R. M. Thorp and Dr. R. J. Walsh. The late Sir Archibald Collins was also a member, and his firm moral support and mature advice are greatly missed.

**Projects in Hand.**—The annual report of the Branch Committee gives the following information:

**Eclampsia Survey:** At the suggestion of Professor Mayes, the Committee has obtained some statistics as to the incidence of eclampsia in general practice. The circular regarding this was directed to all members of the Faculty and asked them to seek the co-operation of non-member colleagues practising in their locality. The committee is particularly grateful to Dr. R. M. Allport, of Gulgong, who obtained figures from all the practitioners in his area of the State. The information received will be published as soon as outstanding returns come in. To date about 4500 confinements have been recorded, with the incidence of three cases of eclampsia.

**Hepatitis Survey:** A more extensive project has been undertaken to obtain information regarding infective hepatitis. The Committee hopes to get some ideas as to the epidemiology of this disease and the clinical picture as seen in general practice. The questionnaire regarding this has been sent so far only to those who are in the Research Register. This will be extended to other members of the Faculty if they are interested in co-operating. The Committee would be pleased to have offers of help from any member who is willing to complete reports on cases he has seen or sees in the coming months.



Thanks are expressed to Dr. Lancaster, who has obtained statistics as to the actual incidence of cases of hepatitis notified in this State in the past eighteen months. These will be published as an additional part of the survey, or possibly earlier, as a separate contribution.

Conclusion: In concluding this report, the Committee would once again stress the important contribution that the general practitioner can make to medical knowledge by "research in the field". He, more than anyone, sees disease in its natural habitat and is in a position to observe simple scientific facts about it. It is to encourage and assist him in recording these facts that the research activities of the College can play a useful part in medicine.

Any practitioner desiring further information may write to Dr. J. G. Radford (who is honorary secretary of the Research Committee of the New South Wales Faculty of the College of General Practitioners), 24 Carr Street, Coogee, New South Wales.

## Medical Societies.

### THE MEDICAL SCIENCES CLUB OF SOUTH AUSTRALIA.

A MEETING of the Medical Sciences Club of South Australia was held in the New Medical School, Frome Road, Adelaide, on June 3, 1955.

#### Fluoroacetate Toxicity in Sheep.

I. JARRETT and A. PACKHAM, in a paper on fluoroacetate toxicity in sheep, outlined the biochemical lesion associated with fluoroacetate poisoning and briefly reviewed the development of the hypothesis that a metabolic block was present in the tricarboxylic acid cycle, due to inhibition of aconitase. They presented details of the continued administration of sub-lethal doses of fluoroacetate to sheep on various diets. They said that adult sheep receiving 800 grammes of lucerne chaff or 800 grammes of wheat chaff and 100 grammes of gluten and two milligrammes of fluoroacetate per day by drench did not develop signs of poisoning; whereas sheep receiving 800 grammes of wheat chaff alone lost appetite and showed signs of muscular incoordination and convulsions after they had been drenched with fluoroacetate for ten to twenty days. Contrary to reports of the action of fluoroacetate in other animals, it appeared that, in the ruminant, toxicity of sub-lethal doses might vary with the diet, and also with the route of administration. The possible mechanisms associated with the protection of lucerne and gluten were discussed.

#### Principles of Control of Soil-Borne Diseases.

N. T. FLENTJE presented a paper on principles of control of soil-borne diseases. He said that the interaction between a host and a soil-borne pathogen was influenced not only by the physical and chemical factors of the environment, but also by the activity of all the other members of the soil microflora. Synecological studies of the soil microflora had proved extremely difficult, partly because of the lack of suitable techniques, and plant pathologists had concentrated more on autecological studies, disregarding almost all the soil microorganisms other than the actual pathogen. However, one trend now was as far towards a synecological study of the host pathogen interaction as the present limited knowledge of the soil population allowed. The current approaches to the problem of control could be summarized in the following way: (i) Directed at the host plant: (a) resistant varieties, (b) seed protectants, (c) systemic fungicides. (ii) Directed at the pathogen: (a) exclusion by quarantine, (b) reduction in population in soil by chemicals or by using living or dead plant material, (c) use of physical factors in the environment unfavourable to the pathogen.

Mr. Flentje said that his own interest was centred mainly on an investigation of the factors which influenced the population and activity of the pathogen in the rhizosphere, on the actual surface of the host plant and immediately following infection of the host by the pathogen. There was evidence from many sources that germinating seed or a growing plant excreted chemicals into the soil which influenced the activity of a range of soil-borne organisms including pathogenic ones. On the other hand, closely related strains of a particular pathogen varied considerably in their post-penetration reaction with a plant. An under-

standing of those effects would contribute much to the control of the pathogens either directly or indirectly through disease-resistance breeding.

## Out of the Past.

*In this column will be published from time to time extracts, taken from medical journals, newspapers, official and historical records, diaries and so on, dealing with events connected with the early medical history of Australia.*

### THE CLIMATE OF SYDNEY COVE.<sup>1</sup>

[From "A Narrative of the Expedition to Botany Bay", by Watkin Tench, Captain of Marines.]

THE climate is undoubtedly very desirable to live in. In summer the heats are usually moderated by the sea breeze which sets in early; and in winter the degree of cold is so slight as to occasion no inconvenience: once or twice we have had hoar frosts but no appearance of snow.

The thermometer has never risen beyond 84 nor fallen lower than 35; in general it stood in the beginning of February at between 78 and 74 at noon. Nor is the temperature of the air less healthy than pleasant. Those dreadful putrid fevers by which new countries are so often ravaged are unknown to us: and excepting a slight diarrhoea which prevailed soon after we had landed and was fatal in very few instances, we are strangers to epidemic diseases.

On the whole (thunderstorms in the hot months excepted) I know not one climate equal to this I write in. Ere we had been a fortnight on shore we experienced some storms of thunder accompanied with rain, than which nothing could be conceived more violent or tremendous and their repetition for several days, joined to the damage they did by killing several of our sheep, led us to draw presages of an unpleasant nature.

Happily however for several months we have escaped any similar visitations.

## Correspondence.

### THE MEDICAL SERVICE OF PAPUA AND NEW GUINEA.

SIR: I would like, if I may, to comment on the article by Dr. W. L. Calov, which appeared in THE MEDICAL JOURNAL OF AUSTRALIA of August 20. The article is excellent, and gives a most accurate description of the work in the Territory. Any student or practitioner contemplating service in Papua/New Guinea will not be misled by the picture set out in this article.

I would like, if I may, to comment briefly on the place of missions in the medical scheme. Being a comparative newcomer, I cannot speak with wide authority, but if my generalizations from two medical stations are of use, I bring them for what they are worth.

I was fortunate in being associated for two months recently with the Lutheran Hospital at Madang—this hospital houses over 250 in-patients, and is staffed by two doctors and five European nurses, besides native doctor "boys" and "girls". I have worked with these, and the better of the boys—for instance, the laboratory technician—would put some Australian counterparts to shame; and as theatre "sisters" they are all that could be desired. Of course, as your article states, they are not all like that, especially in the highlands, where European influence has more recently penetrated.

Dr. Calov states: "The missions . . . could do more than they are doing." True. The reasons? Firstly, as he states, "Funds are limited"—and this in spite of exceedingly generous supplies of drugs and equipment by the Health Department, plus subsidies paid to the missions for the services of doctors and nurses. And secondly, if the Government is unable to obtain doctors, how much more so the

<sup>1</sup> From the original in the Mitchell Library, Sydney.

missions, able to offer only a small fraction of the salary? And, too, as Dr. Calov says, "they feel, of course, that their first task is to carry the Gospel to the natives"; and, just as at home, only a small minority feels that its Christianity constrains it to enter such work, even so, a doctor must embrace his faith to a like extent to be prepared to serve on a mission. Indeed, this mission counts itself fortunate, amongst a population of roughly 9000, to have a doctor, seven nurses and a 100-bed hospital.

Once again, let me state my appreciation of an excellent report and editorial policy.

Yours, etc.,

JOHN B. HUGHES, M.B., B.S. (Adelaide).

Tinsley Memorial Hospital,  
Australian Baptist Mission,  
Banjer River,  
Via Lae, T.N.G.  
September 26, 1955.

#### ADVERTISEMENTS AND SAMPLES FROM DRUG HOUSES.

SIR: I, too, like Dr. Loorham, would like my name to be taken off the mailing lists of the various drug houses, as I have been retired from practice now for some years. Although I have written to many of them with this request, still some keep on sending their literature.

Yours, etc.,

J. G. AVERY.

Casterton,  
Victoria,  
September 27, 1955.

#### A MEDICAL HISTORY OF THE WOLLONGONG DISTRICT.

SIR: I would draw your attention to some minor inaccuracies in Dr. H. Lee's article, published in our journal of September 3. Referring to myself he writes: "I built a house there (Port Kembla) and installed an assistant, Dr. Kirkwood. In three years' time I moved him into Wollongong, putting Dr. Geeves in his place."

The above is inaccurate.

I had worked as an assistant to Dr. Lee for a very short time in my first year after graduation. I graduated in May, 1914, and went to Queensland. I was in Bourketown (in the Gulf Country) for their race week when war broke out. A patriot in the bar organized a collection to send a cable to Kitchener: "Bourketown is behind you to a man."

Having subscribed my two bob towards the above cable, I naturally felt obliged to return to Sydney and enlist. However, it was May, 1915, before the military authorities recognized my potential value as a soldier, and I had filled in time as an assistant to Dr. Lee in Wollongong, gaining thereby very valuable experience both in lodge practice and motor cycling.

My influence on the practice had apparently not been as catastrophic as it had been on the bicycle, and whilst in France in 1917 (having gained a lot more experience) I received a letter from Dr. Lee asking me to return to Wollongong and practise in partnership with him. I to live in the "fast developing" town of Port Kembla. I accepted this offer, and on returning from France in 1918 we signed a partnership agreement, and I lived and practised in Port Kembla for six years. However, Port Kembla was not "maturing" as quickly as I was. I moved into Wollongong, still practising in partnership with Dr. Lee, and we conjointly employed an assistant who lived at Port Kembla.

Dr. Lee's wording of this portion of his article is unfortunate, but the mistake is so trivial that I had decided to ignore it. However, since the article appeared various old friends have drawn my attention to the statements, and I would be grateful if you would publish this correction.

Apart from a three-year war break, I practised in Wollongong and district from 1914 to 1935. In both professional and personal experience it was a rich and happy time. However, I had been invalided out of France with a severe hearing defect of traumatic origin, and by middle age this had "caught me up" and forced me out of general practice. Hearing aids were not very efficient in 1935.

I might add that when I first went to Wollongong—as assistant to Dr. Lee—there were six doctors in the town: two Dr. Lees, who were father and son; two Dr. Kerrs, who were brothers; and two Dr. Kirkwoods, who were no relation. "Young Harry" and the two Kirkwoods still survive, but only the former in Wollongong. May I congratulate him on the wide scope of his article, which scope may itself excuse the trivial errors to which I have drawn attention.

Yours, etc.,

NOEL E. KIRKWOOD.

Waterview Street,  
Mona Vale,  
New South Wales.  
October 4, 1955.

#### CONVENIENT BACTERIOLOGICAL SERVICES.

SIR: The desirability or feasibility of a State service for the examination of bacteriological specimens, as recommended by Dr. Pacy (M. J. AUSTRALIA, August 6, 1955), is open to question; and the information supplied to the clinician by such a service may be rather unreliable for many technical reasons.

A State postal service for the histological examination of surgical specimens does, however, operate in Nova Scotia, Canada, a Province with a population of 650,000. There, the histological examination of surgical specimens is a free State service and is performed by the Provincial Government Pathologist at a central laboratory. All tissues surgically removed, whatever their relative importance clinically, are submitted for examination, firstly because the service is free and secondly because failure to do so would result in loss of American Medical Association "accreditation" of the hospital concerned. Any particular hospital, of course, still retains the right to appoint its own surgical pathologist in lieu of this service, but in practice that does not occur because of the shortage of pathologists.

Suitable containers, consisting of a glass inner jar and a stout outer cardboard cylinder with metal screw ends, are sent by the Health Department, free of charge, to all hospitals in the Province, in quantities and at intervals determined by experience. This is done automatically from a special department, without the necessity of a requisition. These jars and containers are supplied in various suitable sizes. They are labelled with the address of the central laboratory and require no outer wrapping. Breakages do not occur.

The surgical specimens from this population of 650,000 amount to about 15,000 annually and are sent from regions as far as 270 miles distant by train and passenger bus. Within forty-eight hours of receipt of the specimen, the pathologist's report is in the post, and if the history accompanying the specimen suggests that further treatment is required, the report is telephoned. This procedure presents no problem in Canada, where a trunk call can be obtained almost as rapidly as a local call. In all cases where the biopsy specimen is from a malignant tumour the report is also telephoned, in many instances after the examination of a frozen section performed soon after receipt.

Yours, etc.,

C. E. MARSHALL.

Department of Pathology,  
Dalhousie University,  
Halifax, N.S.,  
Canada.  
September 30, 1955.

#### STANDARDIZATION OF HOSPITAL FORMULARIES.

SIR: The appeal of Dr. Ronald Lowe (M. J. AUSTRALIA, September 24, 1955) for cooperation on a national rather than on an institutional level in the matter of the compilation of hospital formularies merits serious consideration. Most hospital formularies contain comparable prescriptions, which, while bearing the same name, often differ slightly and insignificantly in their constitution and in the doses of their active ingredients. This leads to much unnecessary confusion, and without doubt undermines public confidence when a prescription, bearing a title common to many formularies but without reference to a particular one, is dispensed differently within the limits of the same city and State.

In Victoria, the acceptance in principle of the adoption of the Australian Pharmaceutical Formulary as a basic hospital formulary has been agreed to by representatives of all the major public hospitals and the Hospital and Charities Board. The frank acceptance in fact of this work by the Victorian Eye and Ear Hospital gives an admirable and practical lead.

The idea of the adoption of a formulary on a nation-wide basis is not a new one, and its practicability was amply demonstrated in the harmonious acceptance of the Australian War Pharmacopoeia in a recent national crisis. The National Formulary of Great Britain, elaborated by a joint committee representative of the medical and pharmaceutical professions, first appeared in 1949 and has run to two subsequent editions.

The new edition of the Australian Pharmaceutical Formulary has, I believe, all the elements which are compatible with its acceptance on an Australia-wide scale, and in Victoria its legal status is such that it takes precedence over the British Pharmaceutical Codex and over all hospital pharmacopoeias where reference to the source of a formula is not specifically stated. In its preparation, Formulary revision committees, representing official pharmacy in each State, keep close observation on local prescribing practices and on the advent of new drugs which require pharmaceutical skill for their presentation in suitable forms for effective administration. The deliberations and observations of each committee are forwarded to all other State revision committees, and after a full exchange of views, tentative formulae are established and critically reviewed for their efficiency, compatibility and stability under varying conditions of climate throughout Australia.

Though much guidance and encouragement are given these workers by interested medical confrères, the time is now ripe for the formation of definite committees, representing both professions, to establish a National Formulary with ample provision for progressive addenda and complete periodic revision at stated intervals. Such a formulary would automatically satisfy the need for a basic formulary by hospitals throughout Australia. Each individual hospital would necessarily have its own limited formulary for its special requirements, but these would be potentially local supplements, the formulae of which would be submitted periodically to the central revision body for possible inclusion in subsequent editions of the National Formulary.

In the meantime, the Australian Pharmaceutical Formulary (A.P.F.) is an established work, of scope sufficiently wide to satisfy the basic requirements of medical practice, and, we believe, of sufficient merit to satisfy at once a national need.

As a start it would be possible to consider this matter at meetings of State medico-pharmaceutical liaison committees for introduction to the controlling bodies of both professions.

Yours, etc.,

71 Collins Street,  
Melbourne,  
September 28, 1955.

BYRON STANTON.

## Post-Graduate Work.

### THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

#### Week-End Course at Cooma and Bega.

THE Post-Graduate Committee in Medicine in the University of Sydney announces that, in conjunction with the Far South Coast and Tablelands Medical Association, a week-end course will be held at Cooma and Bega from Thursday to Sunday, November 17 to 20, 1955. The programme is as follows:

Thursday, November 17, at the Cooma District Hospital: 7.45 a.m., registration; 8 a.m., practical demonstrations of anæsthetic machine, Dr. L. T. Shea.

Friday, November 18, at the Bega District Hospital: 8 a.m., practical demonstrations of anæsthetic machine, Dr. L. T. Shea.

Saturday, November 19, at the Country Women's Association Rooms, Bega: 2 p.m., registration; 2.15 p.m., "Head Injuries", Dr. Douglas Miller; 4.15 p.m., "The Management of Diabetes with Special Reference to the New Insulins", Dr. Hales Wilson.

Sunday, November 20, at the Country Women's Association Rooms, Bega: 9.30 a.m., "An Anæsthetist Returns to General Practice", Dr. L. T. Shea; 11.15 a.m., "Brachial Neuralgia", Dr. Douglas Miller; 2 p.m., "Meningitis", Dr. Hales Wilson; 3.45 p.m., "Some Anæsthetic Hazards", Dr. L. T. Shea.

Fee for attendance at the course will be £3 3s. Those wishing to attend are requested to notify Dr. E. C. Blomfield, honorary secretary of the course, 104 Gipps Street, Bega (telephone: Bega 82), as soon as possible.

### TRAINING IN PSYCHIATRY AT MCGILL UNIVERSITY.

THE Department of Psychiatry, McGill University, Montreal, Canada, has a limited number of openings for training, and applications are now being considered. Applicants must have graduated from an approved medical school and have had a general internship of one year.

The four-year diploma course provides general basic preparation during the first two years. The last two years provide special patterns of instruction for those: (a) planning to enter the field of general hospital, community or university psychiatry; (b) preparing themselves for a career in child psychiatry; (c) intending to enter the field of research psychiatry.

Credit may be allowed for previous training.

Shorter periods of instruction may be arranged, as well as instruction in special fields.

Full training in psychoanalysis also may be undertaken within the department of psychiatry by suitably prepared candidates. Separate application for this training is required.

All those accepted for training are assigned to one of the seven teaching centres in Montreal. These positions carry with them board and lodging, or, in lieu of lodging, a living-out allowance together with an honorarium ranging from \$40 to \$100 a month, depending upon the clinical position to which the applicant is assigned. For those in the advanced years of the course, clinical positions carrying higher salaries are available. In several centres, additional emoluments of \$1800 a year are available, mainly in the form of bursaries, these being issued under certain conditions in regard to which information will be given on request.

Applicants should write to the Chairman of the Department of Psychiatry, McGill University, Montreal, Canada.

## The College of Radiologists of Australasia.

### EXAMINATIONS FOR DIPLOMA.

THE Honorary Secretary of the College of Radiologists of Australasia has advised that examinations for Part I of the diploma qualification may be taken in diagnostic and/or therapeutic radiology, and will commence on March 19, 1956, and August 27, 1956, respectively. Examinations in Part I will be held in the capital cities of States in which candidates are resident, and in New Zealand cities by arrangement.

All candidates in Australia presenting for Part II must attend in Melbourne for both written and practical examinations for the March series, which will commence on March 19, 1956, and in Sydney for both written and practical examinations for the August series, which will commence on August 27, 1956, and which will, if possible, be completed within one week. New Zealand candidates are to attend at a centre to be selected in New Zealand.

Entry forms must be received at the College office in Sydney not later than January 23, 1956, for the March series, and July 2, 1956, for the August series, accompanied by the entry fee and all the necessary certificates. Incomplete entry forms or lack of appropriate certificates will cause rejection of the candidate's application.

Entry forms, together with a brochure of information containing the syllabus for the examinations, are available on request from the Secretary of the College of Radiologists of Australasia, 135 Macquarie Street, Sydney, and also an additional sheet of information referable to examination details for the 1956 examinations.



The acquisition of the diploma entitles the holder to apply for membership of the College.

## University Intelligence.

### THE UNIVERSITY OF SYDNEY.

#### Medical Research Fellowships.

APPLICATIONS are invited for the following medical research fellowships for the year 1956. Fellowships are renewable for a second and, in certain circumstances, for a third year.

The Reginald Maney Lake Scholarship and Amy Laura Bonamy Scholarship are for pathological research work, have a value of £1252 *per annum* and fall due on January 1, 1956.

The Anderson Stuart Fellowship and Marion Clare Reddall Scholarship are for research in any branch of medical science, have a value of £1252 *per annum* and fall due on January 1, 1956.

The Liston Wilson Fellowship is for research in spastic paralysis or some closely allied subject, has a value of £1252 *per annum* and falls due on January 1, 1956.

The Dr. Gordon Craig Fellowship is for research in urology, has a value of £600 *per annum* (including hospital residence) and falls due in April, 1956.

The Sister Sanders Scholarship is for part-time research work in the prevention of diseases in children; its value is to be determined; it falls due on January 1, 1956.

Applications for fellowships for 1956 should be made to the Registrar, and will close on November 30, 1955. The fellowships for 1956 will be awarded in December, 1955. Application forms may be obtained from the Registrar's office. Regulations in regard to these research fellowships may be seen in the 1955 Calendar, pages 417 to 421.

### THE UNIVERSITY OF MELBOURNE.

#### Elections: Council and Standing Committee of Convocation.

THE following twelve nominations have been received for five vacancies for representatives of graduates on the Council of the University of Melbourne: Dr. Lucy M. Bryce, Mr. J. G. Burnell, Sir Ian Clunies-Ross, Dr. E. G. Coppel, Dr. J. R. Darling, Dr. C. H. Fitts, Mr. G. E. Fitzgerald, Mr. C. M. Gilray, Mr. W. B. Griffiths, Mr. D. H. Merry, Sir John Newman-Morris, Mr. L. W. Rogers.

The only section of the Standing Committee of Convocation in which there will be an election is for graduates in science, there being six nominations for three vacancies, namely: Dr. C. M. Focken, Dr. F. G. Lennox, Mr. R. E. Paul, Mr. H. B. Sarjeant, Mr. G. S. C. Semmens, Dr. R. C. Traill.

Voting papers will be sent to all graduates whose addresses are known. Graduates who wish to vote and do not receive voting papers by November 5 must apply to the Returning Officer by November 11.

Voting papers must be returned before noon on Wednesday, November 30.

## Medical Practice.

### NATIONAL HEALTH ACT.

THE following notice appeared in the *Commonwealth of Australia Gazette* of October 13, 1955.

#### NATIONAL HEALTH ACT, 1953.

##### Part VII.—Pharmaceutical Benefits: Suspension of Medical Practitioner.

I, EARLE PAGE, the Minister of State for Health, hereby give notice, in pursuance of sub-section (1.) of section 96 of the *National Health Act*, 1953, that I have suspended for one month as from 16th September, 1955, the authority under

#### DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED OCTOBER 8, 1955.<sup>1</sup>

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism .. ..	1	..	1(1)	..	..	..	..	..	2
Anthrax .. ..	..	..	..	..	..	..	..	..	..
Ancylostomiasis .. ..	..	..	..	..	..	..	..	..	..
Cholera .. ..	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus) .. ..	..	..	..	..	..	..	..	..	..
Dengue .. ..	..	..	..	..	..	..	..	..	..
Diarrhoea (Infantile) .. ..	3(2)	8(7)	6(2)	..	..	..	..	2	19
Diphtheria .. ..	1	..	1(1)	..	6(6)	..	..	..	8
Dysentery (Bacillary) .. ..	..	1	..	..	..	..	..	..	1
Encephalitis .. ..	2(1)	1(1)	..	..	..	..	..	..	3
Filaria .. ..	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice .. ..	..	1	..	..	..	..	..	..	2
Hydatid .. ..	..	..	..	..	..	1(1)	..	..	142
Infective Hepatitis .. ..	37(13)	79(38)	8	16(3)	8(4)	1	..	1	3
Lead Poisoning .. ..	..	..	3	..	..	..	..	..	1
Leprosy .. ..	..	..	13	..	..	..	1	..	13
Leptospirosis .. ..	..	..	..	..	..	..	..	..	1
Malaria .. ..	..	1	..	..	1	1	..	..	3
Meningococcal Infection .. ..	..	..	..	..	..	..	..	..	..
Ophthalmia .. ..	..	..	..	..	..	..	..	..	..
Ornithosis .. ..	..	..	..	..	..	..	..	..	..
Paratyphoid .. ..	..	..	..	..	..	..	..	..	..
Plague .. ..	..	..	..	..	..	..	..	..	..
Polymyositis .. ..	6(3)	1	1	..	..	..	..	..	9
Puerperal Fever .. ..	1	..	3(5)	..	..	..	..	..	9
Rubella .. ..	..	61(47)	1	3(3)	1(1)	..	..	..	66
Salmonella Infection .. ..	..	..	..	..	..	..	..	..	..
Scarlet Fever .. ..	7(5)	15(10)	17(9)	6(2)	2(2)	1	..	..	48
Smallpox .. ..	..	..	..	..	..	..	..	..	..
Tetanus .. ..	..	..	..	..	..	..	..	..	..
Trachoma .. ..	..	..	..	..	9(9)	..	..	..	9
Trichinosis .. ..	..	..	..	..	..	..	..	..	..
Tuberculosis .. ..	27(17)	23(14)	17(12)	3(2)	5(3)	2(2)	2	..	79
Typhoid Fever .. ..	..	..	..	..	..	..	..	..	..
Typhus (Flea-, Mite- and Tick-borne) .. ..	..	..	4	..	1(1)	..	..	..	5
Typhus (Louse-borne) .. ..	..	..	..	..	..	..	..	..	..
Yellow Fever .. ..	..	..	..	..	..	..	..	..	..

<sup>1</sup> Figures in parentheses are those for the metropolitan area.

section 88 of the said Act of Jeremiah John O'Connor of George Street, Scarborough, Western Australia, medical practitioner, to write a prescription for the supply of pharmaceutical benefits following investigation and report by the Medical Services Committee of Inquiry for the State of Western Australia established under the *National Health Act*, 1953, concerning the conduct of the aforesaid medical practitioner in relation to his authority and the provisions of the regulations under the said Act.

Dated this twenty-seventh day of September, 1955.

EARLE PAGE,  
Minister of State for Health.

### Medical Appointments.

Under the provisions of the *Quarantine Act*, 1908-1950, Dr. Aksel Ivanov has been appointed as Quarantine Officer, Queensland.

Dr. J. Bell has been appointed Government medical officer at Bowen in the Department of Health and Home Affairs, Queensland.

Dr. O. W. Powell has been authorized to sign permissions and certificates for cremation, and to grant permission to cremate any human body after death, under the provisions of *The Cremation Acts*, 1913 to 1935, of Queensland.

Dr. Peter Roylance Delamothe has been appointed Quarantine Officer at Bowen, Queensland, under provisions of the *Quarantine Act*, 1908-1950.

Dr. Joseph Robinson has been appointed Quarantine Officer, Northern Territory, under the provisions of the *Quarantine Act*, 1908-1950.

Dr. M. E. Lindon has been appointed honorary clinical assistant to the Medical Section at the Royal Adelaide Hospital.

Dr. J. L. Hayward has been appointed honorary physician at the Royal Adelaide Hospital.

John Michael Thompson has been appointed Quarantine Officer under the provisions of the *Quarantine Act*, 1908-1950.

Under the provisions of the *Quarantine Act*, 1908-1950, the medical officer at present acting as State Medical Officer at Derby, Western Australia, has been appointed Quarantine Officer at Derby, Western Australia.

Dr. B. J. Shea has been appointed deputy superintendent at the Parkside Mental Hospital in the Hospitals Department, South Australia.

### Nominations and Elections.

THE undermentioned have applied for election as members of the South Australian Branch of the British Medical Association:

Chapman, Gilbert Wesley, qualified 1955, Inglewood, South Australia.

Bawden, Maxwell George, qualified 1954, 26 Aloha Terrace, Black Forest, South Australia.

Meldrum, Brian Reginald, qualified 1952, Ardrossan, South Australia.

The undermentioned have been elected as members of the South Australian Branch of the British Medical Association: Dietman, Clarence Charles, qualified 1954; Kent, Norma Claire Campbell, M.B., Ch.B. (N.Z.), 1946, Ph.D. (Cantab.), 1955.

The undermentioned has applied for election as a member of the New South Wales Branch of the British Medical Association:

De Marchi, Mario, registered in accordance with the provisions of Section 17 (2) of the *Medical Practitioners Act*, 1938-1955, M.D. (Rome), 1930, T.B. Centre, P.O. Box 30, Ramna, Dacca, East Pakistan.

The undermentioned have been elected as members of the New South Wales Branch of the British Medical Association: Bowdler, John Denby, M.B., B.S., 1955 (Univ. Sydney); Leigh, Boyd Lionel Hilton, M.B., B.S., 1955 (Univ. Sydney);

Brunton, Lawrence Jackson, M.B., 1945 (Univ. Sydney); Eichel, Ferdinand, registered in accordance with the provisions of Section 17 (1) (c) of the *Medical Practitioners Act*, 1938-1955; Herz, Leopold Max, registered in accordance with the provisions of Section 17 (1) (c) of the *Medical Practitioners Act*, 1938-1955.

### Deaths.

THE following deaths have been announced:

BEARE.—Frank Howard Beare, on October 9, 1955, at Adelaide.

LAWSON.—James Adrian Lawson, on October 16, 1955, at Auburn, New South Wales.

QUINN.—Reginald George Quinn, on October 17, 1955, at Brisbane.

### Diary for the Month.

Nov. 1.—New South Wales Branch, B.M.A.: Organization and Science Committee.

Nov. 2.—Western Australian Branch, B.M.A.: Branch Council.

Nov. 8.—New South Wales Branch, B.M.A.: Executive and Finance Committee.

### Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

*New South Wales Branch* (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.

*Queensland Branch* (Honorary Secretary, B.M.A. House, 225 Wickham Terrace, Brisbane, B17): Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

*South Australian Branch* (Honorary Secretary, 80 Brougham Place, North Adelaide): All contract practice appointments in South Australia.

*Western Australian Branch* (Honorary Secretary, 205 Saint George's Terrace, Perth): Norseman Hospital; all contract practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

### Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: MW 2651-2-3.)

Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this journal. The management cannot accept any responsibility or recognize any claim arising out of non-receipt of journals unless such notification is received within one month.

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